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(54) Title: SMALL STREPTOCOCCUS PYOGENES ANTIGENS AND THEIR USE

(57) Abstract: The present invention relates to a peptide consisting of one antigen of *Streptococcus pyogenes* (*S. pyogenes*) of any of the SEQ ID NOS: 1 to 7 or a functional active variant thereof, optionally further consisting of additional amino acid residue(s); a nucleic acid coding for the same; a pharmaceutical composition, especially a vaccine, comprising said peptide or said nucleic acid; an antibody or functional active fragment thereof specifically binding to the antigen; a hybridoma cell line which produces said antibody; a method for producing said antibody; a pharmaceutical composition comprising said antibody; the use of said peptide or said nucleic acid for the manufacture of a medicament for the immunization or treatment of a subject; the use of said antibody or functional fragment thereof for the manufacture of a medicament for the treatment of an infection; a method of diagnosing a *S. pyogenes* infection; a method for identifying a ligand capable of binding to said peptide; and the use of said peptide for the isolation and/or purification and/or identification of an interaction partner of the peptide.

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Small *Streptococcus pyogenes* Antigens and their Use

- 5 The present invention relates to a peptide consisting of one antigen of *Streptococcus pyogenes* (*S. pyogenes*) of any of the SEQ ID NOS: 1 to 7 or a functional active variant thereof, optionally further consisting of additional amino acid residue(s); a nucleic acid coding for the same; a pharmaceutical composition, especially a vaccine, comprising said peptide or said nucleic acid; an antibody or functional active fragment thereof specifically
10 binding to the antigen; a hybridoma cell line which produces said antibody; a method for producing said antibody; a pharmaceutical composition comprising said antibody; the use of said peptide or said nucleic acid for the manufacture of a medicament for the immunization or treatment of a subject; the use of said antibody or functional fragment thereof for the manufacture of a medicament for the treatment of an infection; a method of
15 diagnosing a *S. pyogenes* infection; a method for identifying a ligand capable of binding to said peptide; and the use of said peptide for the isolation and/or purification and/or identification of an interaction partner of the peptide.

20 *Streptococcus pyogenes*, also called group A streptococcus (GAS), is an important gram-positive extracellular bacterial pathogen and commonly infects humans. GAS colonizes the throat or skin and is responsible for a number of suppurative infections and non-suppurative sequelae. It is primarily a disease of children and causes a variety of infections including bacterial pharyngitis, scarlet fever, impetigo and sepsis in humans. Decades of epidemiological studies have led to the concept of distinct throat and skin strains, where
25 certain serotypes are often associated with throat or skin infections, respectively (Cunningham, M. (2000). *Clin Microbiol Rev* **13**: 470-511). GAS has been discovered responsible for streptococcal toxic shock syndrome associated necrotizing fasciitis which is recently resurgent in the USA (Cone, L., et al. (1987). *New Engl J Med* **317**: 146-9; Stevens, D. (1992). *Clin Infect Dis* **14**: 2-11) and has been described as the "flesh eating"
30 bacterium which invades skin and soft tissues leading to tissue or limb destruction.

Several post-streptococcal sequelae may occur in humans subsequent to infection, such as acute rheumatic fever, acute glomerulonephritis and reactive arthritis. Acute rheumatic

fever and rheumatic heart disease are of these the most serious autoimmune sequelae and have led to disability and death of children worldwide. *S. pyogenes* can also causes severe acute diseases such as scarlet fever and necrotizing fasciitis and has been associated with Tourette's syndrome, tics and movement and attention disorders.

5

Group A streptococci are the most common bacterial cause of sore throat and pharyngitis and account for at least 16% of all office calls in a general medical practice, season dependent (Hope-Simpson, R. (1981). J Hyg (Lond) 87: 109-29). It primarily affects children in school-age between 5 to 15 years of age (Cunningham, supra). All ages are 10 susceptible to spread of the organism under crowded conditions, for example in schools. GAS are not considered normal flora though, but pharyngeal carriage of group A streptococci can occur without clinical symptoms.

Group A streptococci can be distinguished by the Lancefield classification scheme of 15 serologic typing based on their carbohydrate or classified into M protein serotypes based on a surface protein that can be extracted by boiling bacteria with hydrochloric acid. This has led to the identification of more than 80 serotypes, which can also be typed by a molecular approach (emm genes). Molecular typing has identified more than 150 individual emm types. Certain M protein serotypes of *S. pyogenes* are mainly associated 20 with pharyngitis and rheumatic fever, while others mainly seem to cause pyoderma and acute glomerulonephritis (Cunningham, supra).

Also implicated in causing pharyngitis and occasionally toxic shock are group C and G streptococci, which must be distinguished after throat culture (Hope-Simpson, supra; 25 Bisno, A., et al. (1987). Infect Immun 55: 753-7).

Currently, streptococcal infections can only be treated by antibiotic therapy. However, 25-30% of those treated with antibiotics show recurrent disease and/or shed the organism in mucosal secretions. There is at present no preventive treatment (vaccine) available to avoid 30 streptococcal infections.

Thus, there remains a need for an effective treatment to prevent or ameliorate streptococcal infections. A vaccine could not only prevent infections by streptococci, but more

specifically prevent or ameliorate colonization of host tissues, thereby reducing the incidence of pharyngitis and other suppurative infections. Elimination of non-suppurative sequelae such as rheumatic fever, acute glomerulonephritis, sepsis, toxic shock and necrotizing fasciitis would be a direct consequence of reducing the incidence of acute infection and carriage of the organism. Vaccines capable of showing cross-protection against other streptococci would also be useful to prevent or ameliorate infections caused by all other beta-hemolytic streptococcal species, namely groups A, B, C and G.

A vaccine can contain a whole variety of different antigens. Examples of antigens are whole-killed or attenuated organisms, subfractions of these organisms/tissues, proteins, or, in their most simple form, peptides. Antigens can also be recognized by the immune system in form of glycosylated proteins or peptides and may also be or contain polysaccharides or lipids. Short peptides can be used since for example cytotoxic T-cells (CTL) recognize antigens in form of short usually 8-11 amino acids long peptides in conjunction with major histocompatibility complex (MHC). B-cells can recognize linear epitopes as short as 4-5 amino acids, as well as three-dimensional structures (conformational epitopes).

In some circumstances, adjuvants may be useful for sustaining antigen-specific immune responses. Primarily, adjuvants are acting, but are not restricted in their mode of action, on so-called antigen presenting cells (APCs). These cells usually first encounter the antigen(s) followed by presentation of processed or unmodified antigen to immune effector cells. Intermediate cell types may also be involved. Only effector cells with the appropriate specificity are activated in a productive immune response. The adjuvant may also locally retain antigens and co-injected other factors. In addition the adjuvant may act as a chemoattractant for other immune cells or may act locally and/or systemically as a stimulating agent for the immune system.

Approaches to develop a group A streptococcal vaccine have focused mainly on the cell surface M protein of *S. pyogenes* (Bessen, D., et al. (1988). *Infect Immun* **56**: 2666-2672; Bronze, M., et al. (1988). *J Immunol* **141**: 2767-2770). Since more than 80 different M serotypes of *S. pyogenes* exist and new serotypes continually arise (Fischetti, V. (1989). *Clin Microbiol Rev* **2**: 285-314), inoculation with a limited number of serotype-specific M

protein or M protein derived peptides will not likely be effective in protecting against all other M serotypes. Furthermore, it has been shown that the conserved region of the M protein contains an amino acid sequence, which is immunologically cross-reactive with human heart tissue, which is thought to account for heart valve damage associated with 5 rheumatic fever (Fenderson, P., et al. (1989). J Immunol **142**: 2475-2481).

There are other proteins under consideration for vaccine development, such as the erythrogenic toxins, streptococcal pyrogenic exotoxin A and streptococcal pyrogenic exotoxin B (Lee, P. K. (1989). J Clin Microbiol **27**: 1890-2). Immunity to these toxins 10 could possibly prevent the deadly symptoms of streptococcal toxic shock, but it may not prevent colonization by group A streptococci.

The use of the above described proteins as antigens for a potential vaccine as well as a number of additional candidates (Ji, Y., et al. (1997). Infect Immun **65**: 2080-2087; 15 Guzman, C., et al. (1999). J Infect Dis **179**: 901-6) resulted mainly from a selection based on easiness of identification or chance of availability. There is a demand to identify efficient and relevant antigens for *S. pyogenes*.

WO 2004/078907 describes a method for identification, isolation and production of 20 hyperimmune serum reactive antigens from *Streptococcus pyogenes*.

The antigens described herein focus on regions shown in the present application to be protective. A suitable antigen size to obtain protection varies based on different factors such as the type of protective epitope (e.g., conformational versus linear) and the number 25 of protective epitopes providing a level of protection. Large antigens containing regions not providing useful protection may be disadvantageous in the context of immunization. First, providing of smaller antigens eases production of the protein in recombinant form. It is generally accepted that it is more difficult to produce larger proteins. Smaller proteins may be produced in a more economic manner, thus saving costs, particularly in the health 30 care system. Second, reducing the size of antigenic proteins used for vaccination may lead to safer products. Eliminating extra sequences in antigenic proteins is desirable, since this reduces the probability of inducing antibodies which can cause cross-reactions with human tissues. Third, proteins used for vaccination may contain more than one antigen, the

antigens directed either against the same disease or against different diseases, in order to obtain a more effective vaccination or vaccination against several diseases. However, if the single antigens are too large a combination into one protein is not feasible.

- 5 Accordingly, one problem underlying the present invention was to provide alternative means for the development of medicaments such as vaccines against *S. pyogenes* infection, particularly smaller proteins.

Surprisingly, the object has been solved by a peptide consisting of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7. These peptides are referred to as antigenic peptides.

15 The sequences of SEQ ID NOS: 1 to 7 are characterized in table 1 of the present specification. The underlying amino acid sequences are disclosed in the attached sequence data. The peptides of SEQ ID NOS: 1 to 7 have been shown to induce an immune response and/or to show protection against *S. pyogenes* in a sepsis and/or lethality model (see 20 Example 1). Functional active variants are obtained by changing the sequence of the antigen as defined below and are characterized by having a biological activity similar to that displayed by the antigen of any of the sequences of SEQ ID NO: 1 to 7 from which it is derived, including the ability to induce immune responses and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model.

25 In some embodiments of the invention the peptide of the invention consists of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7; and
30 a) 1 to 350 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50,

- most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 1; or
- b) 1 to 200 additional amino acid residue(s), preferably 1 to 150, more preferably 1 to 100, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is SEQ ID NO: 2; or
- c) 1 to 100 additional amino acid residue(s), preferably 1 to 75, more preferably 1 to 50, even more preferably at most 1 to 25, still more preferably at most 1 to 10, most preferably 1, 2, 3, 4 or 5 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 3; or
- d) 1 to 150 additional amino acid residue(s), preferably 1 to 100, more preferably 1 to 75, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 4; or
- e) 1 to 450 additional amino acid residue(s), preferably 1 to 300, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 20, 30 or 40 additional amino acids residue(s) if the antigen is SEQ ID NO: 5; or
- f) 1 to 250 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 6 or SEQ ID NO: 7.

The antigen of *S. pyogenes* can be any of the antigens as defined above, namely as defined in any of the SEQ ID NOS: 1, 2, 3, 4, 5, 6 or 7, or a functional active variant thereof, wherein the functional active variant is as defined below.

The antigen or the functional active variant thereof may have added at least one additional amino acid residue heterologous or homologous to the peptide. Homologous refers to any amino acid or amino acid sequence which is identical to the amino acid sequence of the *S. pyogenes* protein from which the antigen is derived, wherein the sequences of SEQ ID NO: 1 to 7 are derived from the following proteins:

Sequence	derived from protein (as disclosed in e.g. WO 2004/078907 or in the attached sequence data)
SEQ ID NO: 1	Spy0269
SEQ ID NO: 2	Spy0292
SEQ ID NO: 3	Spy0292
SEQ ID NO: 4	Spy0416
SEQ ID NO: 5	Spy0416
SEQ ID NO: 6	Spy0416
SEQ ID NO: 7	Spy0872

- In one embodiment the antigen or the functional active variant thereof having one or more additional amino acid residues (see above, particularly as defined in items (a) to (f)) further
- 5 encompasses at least one amino acid residue heterologous to the antigen. The feature "heterologous amino acid" or "amino acid heterologous to the antigen or protein" refers to any amino acid which is different from that amino acid located adjacent to the antigen or protein in any naturally occurring protein of *S. pyogenes*, particularly from that of *S. pyogenes* SF370 (serotype M1). Therefore, the protein of the invention encompassing at
- 10 least one heterologous amino acid refers to a protein which is different from any naturally occurring protein of *S. pyogenes* or fragment thereof, particularly which is different from that of *S. pyogenes* SF370 (serotype M1). The proteins from which the antigens of the invention are derived as well as a reference for their sequences are listed above.
- 15 In certain embodiments, the peptide consists of the antigen, optionally the at least one additional amino acid residue as defined above, and at least one additional heterologous amino acid sequence comprising a marker protein.
- The additional sequence or amino acid residue(s) as defined above consists of (an) amino
- 20 acid residue(s), which may be any amino acid, which may be either an L-and/or a D-amino acid, naturally occurring and otherwise. Preferably the amino acid is any naturally occurring amino acid such as alanine, cysteine, aspartic acid, glutamic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, methionine, asparagine, proline, glutamine, arginine, serine, threonine, valine, tryptophan or tyrosine.

- However, the amino acid residue(s) may also be (a) modified or unusual amino acid(s). Examples of those are 2-amino adipic acid, 3-amino adipic acid, beta-alanine, 2-aminobutyric acid, 4-aminobutyric acid, 6-aminocaproic acid, 2-aminoheptanoic acid, 2-aminoisobutyric acid, 3-aminoisobutyric acid, 2-aminopimelic acid, 2,4-diaminobutyric acid, desmosine, 2,2'-diaminopimelic acid, 2,3-diaminopropionic acid, N-ethylglycine, N-ethylasparagine, hydroxylysine, allo-hydroxylysine, 3-hydroxyproloine, 4-hydroxyproloine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, 6-N-Methyllysine, N-methylvaline, norleucine or ornithine.
- 10 Additionally, the amino acid(s) may be subject to modifications such as posttranslational modifications. Examples of modifications include acetylation, amidation, blocking, formylation, γ -carboxyglutamic acid hydroxylation, glycosilation, methylation, phosphorylation and sulfatation.
- 15 If more than one additional or heterologous amino acid residue is present in the peptide, the amino acid residues may be the same or different from one another.

The antigenic peptide may be flanked by the amino acid residue(s) C-terminally, N-terminally, or C- and N-terminally.

20 In a further embodiment the peptide is as described above in the different embodiments, and contains a region that is essentially identical to any of the antigens of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7, but differs from the antigens of any of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7, in that it is derived from a homologous sequence of a different serotype of *S. pyogenes*, particularly wherein the serotype is M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370.

30 Accordingly, the present invention also relates to antigens of different *S. pyogenes* isolates. Such homologues may easily be identified and isolated based on the nucleic acid and amino acid sequences disclosed herein. A homologous antigen of a different serotype may

be identified by e.g. sequence alignment. The homologous antigen sequence may vary from the antigen of any of the sequences of SEQ ID NO: 1 to 7 by one or more amino acid substitutions, deletions and/or additions. Preferably the homologous antigen sequence has the sequence of any of the homologous variants identified in the attached listing of amino acid sequences.

Examples of homologous sequences of a different serotype are detailed in the attached sequence data. Particularly, sequences homologous to the respective peptide of the invention are those listed below:

10

Full length amino acid sequence (SEQ ID NO)	Peptide of the invention (SEQ ID NO)	Homologous amino acid sequences (SEQ ID NOS)
57	1	58 to 67
68	2	69 to 78
68	3	79 to 88
89	4	90 to 99
89	5	100 to 109
89	6	110 to 119
120	7	121 to 130

There are more than 150 emm types distinguished to date and the typing is based on the variable region at the 5' end of the emm gene (see e.g. Vitali, L., et al. (2002) *J. Clin. Microbiol.* **40**: 679-681). The presence of a homologous antigen can accordingly be determined for every emm type. In addition it is possible to determine the variability of a particular antigen in the various emm types as described for the *sic* gene (Hoe N., et al. (2001) *J. Inf. Dis.* **183**: 633-9). The influence of the various M serotypes on the kind of disease it causes is summarized in a recent review (Cunningham, *supra*). In particular, two groups of serotypes can be distinguished:

20

- 1) Those causing Pharyngitis and Scarlet fever (e.g. M types 1, 3, 5, 6, 14, 18, 19, 24)
- 2) Those causing Pyoderma and Streptococcal skin infections (e.g. M types 2, 49, 57, 59, 60, 61)

This can serve as the basis to identify the relevance of an antigen for the use as a vaccine or in general as a drug targeting a specific disease.

- 5 The information e.g. from the homepage of the Centers for Disease Control and Prevention (CDC) (<http://www.cdc.gov/ncidod/biotech/strep/emmtypes.htm>) gives a dendrogram showing the relatedness of various emm types. Further relevant references are Vitali et al.,
supra (molecular emm typing method), Enright et al., Infection and Immunity 69: 2416-
2427. (2001) (alternative molecular typing method (MLST)), Hoe et al., supra (example for
10 the variation of one antigen (*sic*) in many different serotypes) and Cunningham, supra
(review on GAS pathogenesis). All emm types are completely listed and are available at
publicly available databases (e.g., through the CDC).

In another embodiment of the present invention the variant is a fragment. The fragment is
15 characterized by being derived from the antigen as defined above by one or more amino acid deletions. The deletion(s) may be C-terminally, N-terminally and/or internally. Preferably the fragment is obtained by at most 10, 20, 30, 40, 50, 60, 80, 100, 150 or 200, more preferably by at most 10, 20, 30, 40 or 50, even more preferably at most 5, 10 or 15, still more preferably at most 5 or 10, most preferably 1, 2, 3, 4 or 5 amino acid deletion(s).

- 20 The functional active fragment of the invention is characterized by having a biological activity similar to that displayed by the complete antigen, including the ability to induce immunization and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model. The fragment of an antigen is functional active in the context of the present invention, if the activity of the fragment amounts to at least 10%, preferably at least 25%,
25 more preferably at least 50%, even more preferably at least 70%, still more preferably at least 80%, especially at least 90%, particularly at least 95%, most preferably at least 99% of the activity of the antigen without sequence alteration. These fragments may be designed or obtained in any desired length, including as small as about 50 to 80 amino acids in length.

30

The functional active fragment may be also characterized by other structural features. Accordingly, in one preferred embodiment of the invention the functional active fragments consists of at least 60%, preferably at least 70%, more preferably at least 80%, still more

preferably at least 90%, even more preferably at least 95%, most preferably 99% of the amino acids of the antigen of any of the SEQ ID NOS: 1 to 7. The functional active fragment as defined above may be derived from the peptide by one or more amino acid deletions. The deletions may be C-terminally, N-terminally and/or internally.

5

Another preferred embodiment of the invention relates to a peptide as defined above in the previous embodiments, wherein the antigen is a functional active variant of an antigen of any of the SEQ ID NOS: 1 to 7 and wherein the variant has at least 50% sequence identity to the antigen of any of the SEQ ID NOS: 1 to 7. In a more preferred embodiment the 10 functional active variant has a sequence identity of at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% to the antigen of any of the SEQ ID NOS: 1 to 7.

The percentage of sequence identity can be determined e.g. by sequence alignment. 15 Methods of alignment of sequences for comparison are well known in the art. Various programs and alignment algorithms have been described e.g. in Smith and Waterman, Adv. Appl. Math. 2: 482, 1981 or Pearson and Lipman, Proc. Natl. Acad. Sci. U.S.A. 85: 2444-2448, 1988.

20 The NCBI Basic Local Alignment Search Tool (BLAST) (Altschul et al., J. Mol. Biol. 215: 403-410, 1990) is available from several sources, including the National Center for Biotechnology Information (NCBI, Bethesda, MD) and on the Internet, for use in connection with the sequence analysis programs blastp, blastn, blastx, tblastn and tblastx. Variants of an antigen of any of the sequences of SEQ ID NOS: 1 to 7 are typically 25 characterized using the NCBI Blast 2.0, gapped blastp set to default parameters. For comparisons of amino acid sequences of at least 35 amino acids, the Blast 2 sequences function is employed using the default BLOSUM62 matrix set to default parameters, (gap existence cost of 11, and a per residue gap cost of 1). When aligning short peptides (fewer than around 35 amino acids), the alignment is performed using the Blast 2 sequences 30 function, employing the PAM30 matrix set to default parameters (open gap 9, extension gap 1 penalties). Methods for determining sequence identity over such short windows such as 15 amino acids or less are described at the website that is maintained by the National

Center for Biotechnology Information in Bethesda, Maryland
(<http://www.ncbi.nlm.nih.gov/BLAST/>).

The functional active variant of an antigen is obtained by sequence alterations in the antigen, wherein the antigen with the sequence alterations retains a function of the unaltered antigen, e.g. having a biological activity similar to that displayed by the complete antigen, including the ability to induce an immune response and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model. Such sequence alterations can include, but are not limited to, conservative substitutions, deletions, mutations and insertions. These characteristics of the functional active variant can be assessed e.g. as detailed in Example 1. In the context of the present invention a variant specifically has a biological activity similar to that displayed by the antigen without alteration, including the ability to induce an immune response and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model if the activity of the variant amounts to at least 10%, preferably at least 25%, more preferably at least 50%, even more preferably at least 70%, still more preferably at least 80%, especially at least 90%, particularly at least 95%, most preferably at least 99% of the activity of the antigen without sequence alterations.

The term "functional active variant" includes naturally-occurring allelic variants, as well as mutants or any other non-naturally occurring variants. As is known in the art, an allelic variant is an alternate form of a (poly)peptide that is characterized as having a substitution, deletion, or addition of one or more amino acids that does essentially not alter the biological function of the polypeptide. By "biological function" is meant a function of the polypeptide in the cells in which it naturally occurs, even if the function is not necessary for the growth or survival of the cells. For example, the biological function of a porin is to allow the entry into cells of compounds present in the extracellular medium. The biological function is distinct from the antigenic function. A polypeptide can have more than one biological function.

Within any species of the living world, allelic variation is the rule. For example, any bacterial species, e.g. *S. pyogenes*, is usually represented by a variety of strains (characterized by clonal reproduction) that differ from each other by minor allelic variations. Indeed, a polypeptide that fulfils the same biological function in different

strains can have an amino acid sequence that is not identical in each of the strains. Such an allelic variation is equally reflected at the polynucleotide level.

Allelic variation is very common within the *S. pyogenes* species. Such allelic variation is also the basis for the molecular typing of group A streptococcal strains by emm typing as described above (see, e.g. Facklam, R. et al. (1999) *Emerg Infect Dis.* 5: 247-53 or <http://www.cdc.gov/ncidod/biotech/strep/emmtypes.htm>). Further, genes such as *sic* are subject to allelic variation (Hoe N., et al. (2001) *J. Inf. Dis.* 183: 633-9). However, proteins with large allelic variation are in general not suitable candidates for a vaccine, as immunization would not protect against infection with all strains, or alternative immunization would possibly induce the emergence of new allelic variants not covered by the vaccine.

In a preferred embodiment, the functional active variant or fragment derived from the antigen by amino acid exchanges, deletions or insertions may also conserve, or more preferably improve, the activity (as defined above). Furthermore, these peptides may also cover epitopes, which trigger the same or preferably an improved T cell response. These epitope are referred to as "heteroclitic". They have a similar or preferably greater affinity to MHC/HLA molecules, and the ability to stimulate the T cell receptors (TCR) directed to the original epitope in a similar or preferably stronger manner. Heteroclitic epitopes can be obtained by rational design i. e. taking into account the contribution of individual residues to binding to MHC/HLA as for instance described by (Rammensee, H. et al., 1999, *Immunogenetics.* 50: 213-219), combined with a systematic exchange of residues potentially interacting with the TCR and testing the resulting sequences with T cells directed against the original epitope. Such a design is possible for a skilled man in the art without much experimentation.

In a still more preferred embodiment of the invention the functional active variant of an antigen of any of the SEQ ID NOS: 1 to 7 having at least 50% sequence identity to the antigen of any of the SEQ ID NOS: 1 to 7, especially at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% to the antigen of any of the SEQ ID NOS: 1 to 7 is derived from the antigen of any of the sequences of SEQ ID NOS: 1 to 7 by conservative

substitutions. Conservative substitutions are those that take place within a family of amino acids that are related in their side chains and chemical properties. Examples of such families are amino acids with basic side chains, with acidic side chains, with non-polar aliphatic side chains, with non-polar aromatic side chains, with uncharged polar side chains, with small side chains, with large side chains etc.. In one embodiment, one conservative substitution is included in the peptide. In another embodiment, two conservative substitutions or less are included in the peptide. In a further embodiment, three conservative substitutions or less are included in the peptide.

- 10 Examples of conservative amino acid substitutions include, but are not limited to, those listed below:

	<u>Original Residue</u>	<u>Conservative Substitutions</u>
	Ala	Ser
15	Arg	Lys
	Asn	Gln; His
	Asp	Glu
	Cys	Ser
	Gln	Asn
20	Glu	Asp
	His	Asn; Gln
	Ile	Leu, Val
	Leu	Ile; Val
	Lys	Arg; Gln; Asn
25	Met	Leu; Ile
	Phe	Met; Leu; Tyr
	Ser	Thr
	Thr	Ser
	Trp	Tyr
30	Tyr	Trp; Phe
	Val	Ile; Leu

Examples of suitable variants of the peptide of the invention obtained by one or more amino acid exchange(s), deletion(s) and/or insertion(s) may be derived from data provided in tables 5 to 7 and 9. Particularly, tables 5 to 7 and 9 list naturally occurring amino acid alterations (substitutions, insertions, deletions) at particular positions in comparison to *S.*

5 *pyrogenes* SF370.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 1, the variant of the invention may differ from the peptide having SEQ ID NO: 1 by one or more of the

10 alterations identified in table 5.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 2, the variant of the invention may differ from the peptide having SEQ ID NO: 2 by one or more of the

15 alterations identified in table 6.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 3, the variant of the invention may differ from the peptide having SEQ ID NO: 3 by one or more of the

20 alterations identified in table 6.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 4, the variant of the invention may differ from the peptide having SEQ ID NO: 4 by one or more of the

25 alterations identified in table 7.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 5, the variant of the invention may differ from the peptide having SEQ ID NO: 5 by one or more of the

30 alterations identified in table 7.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 6, the variant of

the invention may differ from the peptide having SEQ ID NO: 6 by one or more of the alterations identified in table 7.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 7, the variant of the invention may differ from the peptide having SEQ ID NO: 7 by one or more of the alterations identified in table 9.

It should be understood that variants obtained from a peptide of the invention by one or more sequence alterations in accordance with tables 5 to 7 and 9 are preferred.

A further aspect of the present invention describes a peptide comprising an amino acid sequence with at least 95% sequence identity to at least one of SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7. In different embodiment the peptide comprises, consists, or consists essentially of a region of at least 95%, at least 97% or at least 99% identical to SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7, or differs by 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid alteration(s). In one embodiment the term "consist" may be as defined in the above items (a) to (f)). Preferably, the peptide does not contain a full-length naturally occurring Spy0269, Spy0292, Spy0416A (amino acids 33-867), or Spy0872.

SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7 provide core sequences useful for producing a protective immune response. SEQ ID NO: 1 provides an amino acid core from amino acids 37-488 of Spy0269. SEQ ID NO: 2 provides a core region of amino acids 23-184 of Spy0292. SEQ ID NO: 3 provides a core of amino acids 23-300 of Spy0292, which is a longer-length sequence containing the shorter-length core sequence of 23-184 of Spy0292 provided in SEQ ID NO: 2. Surprisingly, the shorter fragment Spy0292-1 (SEQ ID NO: 2) shows even greater protection in the mouse model compared to the longer fragment Spy0292-3 (SEQ ID NO: 3), as depicted in Figure 1. As described above, smaller peptides are in general advantageous over larger ones, since they may be produced in a more economic manner, they reduce the probability of inducing antibodies which can cause cross-reactions with human tissues, and they facilitate the preparation of combination vaccines comprising more than one antigen. SEQ ID NO: 4, 5, and 6 provide different Spy0416A core sequences of varying activity. SEQ ID NO: 5 provides a common core of amino acids 148-

458 of Spy0416A and has the lowest activity. SEQ ID NO: 6 provides a core sequence containing amino acids 72-558 of Spy0416A with greater activity than the shorter core. SEQ ID NO: 4 provides an amino acid core containing amino acids 34-677 of Spy0416, also with activity greater than the 148-458 core.

5

Based on the guidance provided herein different peptides can be designed taking into account the core sequences provided in SEQ ID NOs: 1-7. Such guidance includes structurally related peptides containing (1) internal alterations; (2) additional amino acid groups at the amino and/or carboxyl terminus; and/or (3) additional modification(s) as described herein.

10

For structurally related peptides, each amino acid alteration is independently either an addition, substitution, or deletion. In a further embodiment, the amino terminus is methionine. The presence of methionine may be useful for recombinant expression. In some cases, the methionine may be initially present as a result of translation and subsequently cleaved. Additional examples and embodiments, including broader embodiments and some further descriptions applicable for structurally related peptides such as functional variants are provided above, particularly in the description of functional active variants.

15

In another subject of the invention the peptide as described above comprises or consists of at least 2, preferably at least 3, more preferably at least 4 antigens as defined above. If two or more peptides derived from the same full length sequence (e.g Spy0292 or Spy0416) are combined into one peptide, these sequences do preferably not overlap. In one embodiment the term "consist" may be as defined in the above items (a) to (f).

20

In another embodiment of the invention the peptide as defined above may be modified by one or more of a variety of chemical techniques to produce derivatives having essentially the same activity (as defined above for fragments and variants) as the modified peptides, and optionally having other desirable properties. For example, carboxylic acid groups of the protein, whether C-terminal or side chain, may be provided in the form of a salt of a pharmaceutically-acceptable cation or esterified to form an ester, or converted to an amide. Amino groups of the peptide, whether amino-terminal or side chain, may be in the form of

25

- a pharmaceutically-acceptable acid addition salt, such as the HCl, HBr, acetic, benzoic, toluene sulfonic, maleic, tartaric and other organic salts, or may be converted to an amide. Hydroxyl groups of the peptide side chains may be converted to alkoxy or to an ester using well recognized techniques. Phenyl and phenolic rings of the peptide side chains may be substituted with one or more halogen atoms, such as fluorine, chlorine, bromine or iodine, or with alkyl, alkoxy, carboxylic acids and esters thereof, or amides of such carboxylic acids. Thiols can be protected with any one of a number of well recognized protecting groups, such as acetamide groups.
- 10 Peptides of this invention may be in combination with outer surface proteins or other proteins or antigens of other proteins. In such combination, the antigen may be in the form of a fusion protein. The antigen of the invention may be optionally fused to a selected peptide or protein derived from other microorganisms. For example, an antigen or polypeptide of this invention may be fused at its N-terminus or C-terminus to a polypeptide 15 from another pathogen or to more than one polypeptide in sequence. Peptides which may be useful for this purpose include polypeptides identified by the prior art.
- In an embodiment of the invention the peptide of the invention is fused to an epitope tag which provides an epitope to which an anti-tag substance can selectively bind. The epitope 20 tag is generally placed at the amino- or carboxyl-terminus of the peptide but may be incorporated as an internal insertion or substitution as the biological activity permits. The presence of such epitope-tagged forms of a peptide can be detected using a substance such as an antibody against the tagged peptide. Also, provision of the epitope tag enables the peptide to be readily purified by affinity purification using an anti-tag antibody or another 25 type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his), poly-histidine-glycine (poly-his-gly) tags, the HA tag polypeptide, the c-myc tag, the Strep tag and the FLAG tag.
- 30 Fusions also may include the peptides or antigens of this invention fused or coupled to moieties other than amino acids, including lipids and carbohydrates. Further, antigens of this invention may be employed in combination with other vaccinal agents described by the prior art, as well as with other species of vaccinal agents derived from other

microorganisms. Such proteins are useful in the prevention, treatment and diagnosis of diseases caused by a wide spectrum of *Streptococcus* isolates.

These fusion proteins are constructed for use in the methods and compositions of this
5 invention. These fusion proteins or multimeric proteins may be produced recombinantly, or may be synthesized chemically.

The peptides of the invention may be prepared by any of a number of conventional techniques. Desired peptides may be chemically synthesized. An alternative approach
10 involves generating the fragments of known peptides by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes, expressing the digested DNA and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired peptide fragment,
15 by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed as the 5' and 3' primers in the PCR. Techniques for making mutations, such as deletions, insertions and substitutions, at predetermined sites in DNA, and therefore in proteins, having a known sequence are well known. One of skill in the art using conventional techniques, such as PCR, may readily use the antigens and
20 peptides provided herein to identify and isolate other similar proteins. Such methods are routine and not considered to require undue experimentation, given the information provided herein. For example, variations can be made using oligonucleotide-mediated site-directed mutagenesis (Carter et al., *Nucl. Acids Res.*, 13: 4431 (1985); Zoller et al., *Nucl. Acids Res.* 10: 6487 (1987)), cassette mutagenesis (Wells et al., *Gene*, 34: 315 (1985)),
25 restriction selection mutagenesis (Wells et al., *Philos. Trans. R. Soc. London SerA*, 317: 415 (1986)), PCR mutagenesis, or other known techniques can be performed on the cloned DNA to produce the peptide of the invention.

Another subject of the present invention relates to a nucleic acid encoding a peptide of the
30 invention, i.e. any peptide as defined above, or a nucleic acid complementary thereto. Nucleic acid molecules of the present invention may be in the form of RNA, such as mRNA or cRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA e.g. obtained by cloning or produced by chemical synthetic techniques or by a

combination thereof. The DNA may be double-stranded or single-stranded. Single-stranded DNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand. Nucleic acid molecule as used herein also refers to, among other, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded RNA, and RNA that is a mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded, or a mixture of single- and double-stranded regions.

- 10 The nucleic acid may be a fragment of a nucleic acid occurring naturally in *S. pyogenes*, especially in *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, particularly *S. pyogenes* SF370. Preferably the nucleic acid has a sequence as defined in any of the sequences of SEQ ID NOS: 11 to 17 or of any of the homologous variants identified in the attached listing of nucleic acid sequence data. Examples of homologous sequences of a different serotype are those listed below:
- 15

Full length nucleic acid sequence (SEQ ID NO)	Nucleic acid of the invention (SEQ ID NO)	Homologous nucleic acid sequences (SEQ ID NOS)
133	11	134 to 143
144	12	145 to 154
144	13	155 to 164
165	14	166 to 175
165	15	176 to 185
165	16	186 to 195
196	17	197 to 206

- 20 The nucleic acid also includes sequences that are a result of the degeneration of the genetic code. There are 20 natural amino acids, most of which are specified by more than one codon. Therefore, all nucleotide sequences are included in the invention which result in the peptide as defined above.

Additionally, the nucleic acid may contain one or more modified bases. Such nucleic acids may also contain modifications e.g. in the ribose-phosphate backbone to increase stability and half life of such molecules in physiological environments. Thus, DNAs or RNAs with backbones modified for stability or for other reasons are "nucleic acid molecule" as that feature is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as 5 inosine, or modified bases, such as tritylated bases, to name just two examples, are nucleic acid molecule within the context of the present invention. It will be appreciated that a great variety of modifications have been made to DNA and RNA that serve many useful purposes known to those of skill in the art. The term nucleic acid molecule as it is 10 employed herein embraces such chemically, enzymatically or metabolically modified forms of nucleic acid molecule, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including simple and complex cells, *inter alia*. For example, nucleotide substitutions can be made which do not affect the polypeptide encoded by the nucleic acid, and thus any nucleic acid molecule which encodes an antigen 15 or fragment or functional active variant thereof as defined above is encompassed by the present invention.

Furthermore, any of the nucleic acid molecules encoding an antigen of the invention or fragment or functional active variant thereof can be functionally linked, using standard 20 techniques such as standard cloning techniques, to any desired regulatory sequences, whether a *S. pyogenes* regulatory sequence or a heterologous regulatory sequence, heterologous leader sequence, heterologous marker sequence or a heterologous coding sequence to create a fusion protein.

25 The nucleic acid of the invention may be originally formed *in vitro* or in a cell in culture, in general, by the manipulation of nucleic acids by endonucleases and/or exonucleases and/or polymerases and/or ligases and/or recombinases or other methods known to the skilled practitioner to produce the nucleic acids.

30 In one embodiment of the invention the nucleic acid is located in a vector. A vector may additionally include nucleic acid sequences that permit it to replicate in the host cell, such as an origin of replication, one or more desired genes and/or selectable marker genes and other genetic elements known in the art such as regulatory elements directing transcription,

- translation and/or secretion of the encoded protein. The vector may be used to transduce, transform or infect a cell, thereby causing the cell to express inserted nucleic acids and/or proteins other than those native to the cell. The vector optionally includes materials to aid in achieving entry of the nucleic acid into the cell, such as a viral particle, liposome, 5 protein coating or the like. Numerous types of appropriate expression vectors are known in the art for protein expression, by standard molecular biology techniques. Such vectors are selected from among conventional vector types including insects, e.g., baculovirus expression, or yeast, fungal, bacterial or viral expression systems. Other appropriate expression vectors, of which numerous types are known in the art, can also be used for this 10 purpose. Methods for obtaining such expression vectors are well-known (see, e.g. Sambrook et al, Molecular Cloning. A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory, New York (1989)). In one embodiment, the vector is a viral vector. Viral vectors include, but are not limited to, retroviral and adenoviral vectors.
- 15 Suitable host cells or cell lines for transfection by this method include bacterial cells. For example, the various strains of *E. coli* are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Pseudomonas*, *Streptomyces*, and other bacilli and the like may also be employed in this method. Many strains of yeast cells known to those skilled in the art are also available as host cells for expression of the peptides of the 20 present invention. Other fungal cells or insect cells such as *Spodoptera frugiperda* (Sf9) cells may also be employed as expression systems. Alternatively, mammalian cells, such as human 293 cells, Chinese hamster ovary cells (CHO), the monkey COS-1 cell line or murine 3T3 cells derived from Swiss, BALB/c or NIH mice may be used. Still other suitable host cells, as well as methods for transfection, culture, amplification, screening, 25 production, and purification are known in the art.

A peptide of the invention may be produced by expressing a nucleic acid of the invention in a suitable host cell. The host cells can be transfected, e.g. by conventional means such as electroporation with at least one expression vector containing a nucleic acid of the 30 invention under the control of a transcriptional regulatory sequence. The transfected or transformed host cell is then cultured under conditions that allow expression of the protein. The expressed protein is recovered, isolated, and optionally purified from the cell (or from the culture medium, if expressed extracellularly) by appropriate means known to one of

skill in the art. For example, the proteins are isolated in soluble form following cell lysis, or extracted using known techniques, e.g. in guanidine chloride. If desired, the peptides or fragments of the invention are produced as a fusion protein. Such fusion proteins are those described above. Alternatively, for example, it may be desirable to produce fusion proteins
5 to enhance expression of the protein in a selected host cell or to improve purification. The molecules comprising the peptides and antigens of this invention may be further purified using any of a variety of conventional methods including, but not limited to: liquid chromatography such as normal or reversed phase, using HPLC, FPLC and the like; affinity chromatography (such as with inorganic ligands or monoclonal antibodies); size
10 exclusion chromatography; immobilized metal chelate chromatography; gel electrophoresis; and the like. One of skill in the art may select the most appropriate isolation and purification techniques without departing from the scope of this invention. Such purification provides the antigen in a form substantially free from other proteinaceous and non-proteinaceous materials of the microorganism.

15

Another subject of the invention is a pharmaceutical composition, especially a vaccine, comprising

- (i) at least one peptide according to the invention, and/or
- (ii) at least one peptide comprising or consisting of the sequence of any of the SEQ ID
20 NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, or a functional active variant thereof, and
- (iii) optionally a pharmaceutically acceptable carrier or excipient.

The variants of the peptides of (ii) are as defined and may be obtained as the peptides of (i) (see above description of the peptides of the invention). Preferred alterations of the sequences of SEQ ID NO: 8 or 10 are those listed in tables 8 and 9, respectively.

25

The peptides of (i) and (ii) are referred to as pharmaceutical peptides of the invention.

With respect to the peptide of (ii), these proteins have been shown for the first time to be capable to provide protection against lethal *S. pyogenes* challenge (see Example 1),
30 particularly in a physiologically highly relevant intranasal challenge model. Especially protein Spy0895 (SEQ ID NO: 9) shows particular promise as a vaccine candidate, because it provided protection against group A streptococcal infection in all three models listed in Table 1.

A pharmaceutical peptide of the invention may be used for methods for immunizing or treating humans and/or animals with the disease caused by infection with *S. pyogenes*. Therefore, the pharmaceutical peptide may be used within a pharmaceutical composition.

- 5 The pharmaceutical composition of the present invention may further encompass pharmaceutically acceptable carriers and/or excipients. The pharmaceutically acceptable carriers and/or excipients useful in this invention are conventional and may include buffers, stabilizers, diluents, preservatives, and solubilizers. Remington's Pharmaceutical Sciences, by E. W. Martin, Mack Publishing Co., Easton, PA, 15th Edition (1975),
10 describes compositions and formulations suitable for pharmaceutical delivery of the (poly)peptides herein disclosed. In general, the nature of the carrier or excipients will depend on the particular mode of administration being employed. For instance, parenteral formulations usually comprise injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt
15 solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (e. g. powder, pill, tablet, or capsule forms), conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically neutral carriers, pharmaceutical compositions to be administered
20 can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

- In a preferred embodiment the pharmaceutical composition further comprises an immunostimulatory substance such as an adjuvant. The adjuvant can be selected based on
25 the method of administration and may include mineral oil-based adjuvants such as Freund's complete and incomplete adjuvant, Montanide incomplete Seppic adjuvant such as ISA, oil in water emulsion adjuvants such as the Ribi adjuvant system, syntax adjuvant formulation containing muramyl dipeptide, IC31™ (Intercell; a synthetic adjuvant comprising the peptide motif K1.K [WO 02/32451] and an oligonucleotide [WO 01/93905]), or aluminum
30 salt adjuvants. Preferably, the adjuvant is a mineral oil-based adjuvant, most preferably ISA206 (SEPPIC, Paris, France).

In other embodiments the immunostimulatory substance is selected from the group comprising polycationic polymers, especially polycationic peptides such as polyarginine, immunostimulatory deoxynucleotides (ODNs), especially Oligo(dIdC)₁₃, peptides containing at least two LysLeuLys motifs, especially KLKLLLLLK (SEQ ID NO: 55), 5 neuroactive compounds, especially human growth hormone, alum, adjuvants or combinations thereof. In further embodiments, the combination is either a polycationic polymer and immunostimulatory deoxynucleotides or of a peptide containing at least two LysLeuLys motifs and immunostimulatory deoxynucleotides. In a still another embodiment the polycationic polymer is a polycationic peptide.

10

The term "Oligo(dIdC)₁₃" as used in the present invention means a phosphodiester backboned single-stranded DNA molecule containing 13 deoxy (inosine-cytosine) motifs, also defined by the term [oligo-d(IC)₁₃]. The exact sequence is 5'-dIdCIdCIdCIdCIdCIdCIdCIdCIdCIdCIdCIdCIdCIdC-3'. Oligo(dIdC)₁₃ can 15 also be defined by the terms (oligo-dIC₂₆); oligo-dIC₂₆-mer; oligo-deoxy IC, 26-mer; or oligo-dIC, 26-mer, as specified for example in WO 01/93903 and WO 01/93905.

In an embodiment the immunostimulatory substance is at least one immunostimulatory nucleic acid. Immunostimulatory nucleic acids are e.g. neutral or artificial CpG containing nucleic acids, short stretches of nucleic acids derived from non-vertebrates or in form of short oligonucleotides (ODNs) containing non-methylated cytosine-guanine dinucleotides (CpG) in a defined base context (e.g. as described in WO 96/02555). Alternatively, also nucleic acids based on inosine and cytidine as e.g. described in WO 01/93903, or deoxynucleic acids containing deoxy-inosine and/or deoxyuridine residues (described in WO 01/93905 and WO 02/095027) may preferably be used as immunostimulatory nucleic acids in the present invention. Preferably, mixtures of different immunostimulatory nucleic acids are used in the present invention. Additionally, the aforementioned polycationic compounds may be combined with any of the immunostimulatory nucleic acids as aforementioned. Preferably, such combinations are according to the ones described in WO 01/93905, WO 02/32451, WO 01/54720, WO 01/93903, WO 02/13857, WO 02/095027 and WO 03/047602.

In addition or alternatively, such pharmaceutical or vaccine composition may comprise a neuroactive compound. Preferably, the neuroactive compound is human growth factor, e.g. described in WO 01/24822. Also preferably, the neuroactive compound is combined with any of the polycationic compounds and/or immunostimulatory nucleic acids as defined above.

The composition may be used e.g. for immunization or treatment of a subject. The pharmaceutical composition encompasses at least one pharmaceutical peptide of the invention; however, it may also contain a cocktail (i.e., a simple mixture) containing different pharmaceutical peptides (including fragments and other variants) of the invention, optionally mixed with different antigenic proteins or peptides of other pathogens. Such mixtures of these peptides, polypeptides, proteins or fragments or variants thereof are useful e.g. in the generation of desired antibodies to a wide spectrum of Streptococci isolates. The pharmaceutical peptide(s) of the present invention may also be used in the form of a pharmaceutically acceptable salt. Suitable acids and bases which are capable of forming salts with the peptides of the present invention are well known to those of skill in the art, and include inorganic and organic acids and bases.

Still another subject of the invention is a pharmaceutical composition containing a nucleic acid selected from the group consisting of:

- (i) a nucleic acid of the invention and/or a nucleic acid complementary thereto, and/or
- (ii) a nucleic acid coding for the peptide comprising or consisting of the sequence of any of the SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, particularly a DNA sequence of any of the SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20, or a functional active variant thereof or a nucleic acid complementary thereto or the corresponding RNA sequence, and
- (iii) optionally a pharmaceutically acceptable carrier or excipient.

The variants of the nucleic acids of (ii) are as defined and may be obtained as the nucleic acids of (i) (see above description of the nucleic acids of the invention). The nucleic acids of (i) and (ii) are referred to as pharmaceutical nucleic acids of the invention.

The pharmaceutical nucleic acid sequences, alone or in combination with other nucleic acid sequences encoding antigens or antibodies or directed to other pathogenic microorganisms, may further be used as components of a pharmaceutical composition. The composition may be used for immunizing or treating humans and/or animals being
5 susceptible to or having a disease caused by infection with *S. pyogenes*, particularly *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. The pharmaceutically acceptable carrier or excipient may be as defined above.

10

In another embodiment, the pharmaceutical nucleic acids of this invention, alone or in combination with nucleic acid sequences encoding other antigens or antibodies from other pathogenic microorganisms, may further be used in compositions directed to actively induce a protective immune response in a subject to the pathogen. These components of
15 the present invention are useful in methods for inducing a protective immune response in humans and/or animals against infection with *S. pyogenes*, particularly with *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370.

20

For use in the preparation of the therapeutic or vaccine compositions, nucleic acid delivery compositions and methods are useful, which are known to those of skill in the art. The pharmaceutical nucleic acid of the invention may be employed in the methods of this invention or in the compositions described herein as DNA sequences, either administered
25 as naked DNA, or associated with a pharmaceutically acceptable carrier and provide for *in vivo* expression of the antigen, peptide or polypeptide. So-called "naked DNA" may be used to express the antigen, peptide or polypeptide of the invention *in vivo* in a patient. (See, e.g., J. Cohen, Science, 259: 1691-1692, which describes similar uses of "naked DNA"). For example, "naked DNA" associated with regulatory sequences may be
30 administered therapeutically or as part of the vaccine composition e.g., by injection.

Alternatively, a nucleic acid, especially a pharmaceutical nucleic acid according to the invention, encoding an antigen or peptide of the invention or a nucleic acid complementary

thereto may be used within a pharmaceutical composition, e.g. in order to express the antigen or (pharmaceutical) peptide of the invention *in vivo*, e.g., to induce antibodies.

A preferred embodiment of the invention relates to a pharmaceutical composition, wherein
5 the pharmaceutical nucleic acid according to the invention is comprised in a vector and/or a cell. Vectors and cells suitable in the context of the present invention are described above. Vectors are particularly employed for a DNA vaccine. An appropriate vector for delivery may be readily selected by one of skill in the art. Exemplary vectors for *in vivo* gene delivery are readily available from a variety of academic and commercial sources,
10 and include, e.g., adeno-associated virus (International patent application No. PCT/US91/03440), adenovirus vectors (M. Kay et al, Proc. Natl. Acad. Sci. USA, 91: 2353 (1994); S. Ishibashi et al, J. Clin. Invest., 92: 883 (1993)), or other viral vectors, e.g., various poxviruses, vaccinia, etc.. Recombinant viral vectors, such as retroviruses or adenoviruses, are preferred for integrating the exogenous DNA into the chromosome of the
15 cell.

Another subject of the invention relates to an antibody or functional active fragment thereof which binds specifically to the antigen of the invention. The present invention includes, for example, monoclonal and polyclonal antibodies, chimeric, single chain, and
20 humanized antibodies, as well as Fab fragments, or the product of a Fab expression library.

While *S. pyogenes* infections are primarily a disease of children and cause non-severe diseases such as bacterial pharyngitis and impetigo, GAS are also responsible for streptococcal toxic shock syndrome associated necrotizing fasciitis (Cone, L., et al. (1987).
25 New Engl J Med 317: 146-9; Stevens, D. (1992). Clin Infect Dis 14: 2-11) and several post-streptococcal sequelae such as acute rheumatic fever, acute glomerulonephritis and reactive arthritis. It would be very beneficial to provide monoclonal or polyclonal antibody therapies which target antigenic proteins of *S. pyogenes* and have the potential to support a therapy of an infection or eliminate the pathogen and the disease altogether.

30

In a preferred embodiment the antibody is a monoclonal, polyclonal, chimeric or humanized antibody or functional active variant thereof. In another preferred embodiment the functional active fragment comprises a Fab fragment.

Antibodies generated against the antigens, fragments or variants thereof of the present invention can be obtained by direct injection of the antigens, fragments or variants thereof into an animal or by administering the antigens, fragments or variants thereof to an animal, preferably a non-human. The antibody so obtained will then bind the antigens, fragments or variants. Such antibodies can then be used to isolate reactive antigens, fragments or variants thereof from tissue expressing those.

For preparation of monoclonal antibodies, any technique known in the art, which provides antibodies produced by continuous cell line cultures, e.g. a hybridoma cell line, can be used.

Techniques described for the production of single chain antibodies (U. S. Patent No. 4,946,778) can be adapted to produce single chain antibodies to the antigens, fragments or variants thereof according to this invention. Also, transgenic mice or other organisms such as other mammals may be used to express humanized antibodies to antigens, fragments or variants thereof according to this invention.

Still another subject of the invention relates to a hybridoma cell line which produces the antibody of the invention.

Hybridoma cell lines expressing desirable monoclonal antibodies are generated by well-known conventional techniques. The hybridoma cell can be generated by fusing a normal-activated, antibody-producing B cell with a myeloma cell. In the context of the present invention the hybridoma cell is able to produce an antibody specifically binding to the antigen of the invention.

Similarly, desirable high titre antibodies are generated by applying known recombinant techniques to the monoclonal or polyclonal antibodies developed to these antigens (see, e.g., PCT Patent Application No. PCT/GB85/00392; British Patent Application Publication No. GB2188638A; Amit et al., *Science*, 233: 747-753 (1986); Queen et al., *Proc. Natl. Acad. Sci. USA*, 86: 10029-10033 (1989); PCT Patent Application No. WO90/07861;

Riechmann et al., *Nature*, 332: 323-327 (1988); Huse et al., *Science*, 246: 1275-1281 (1988)).

The present invention also provides a method for producing an antibody according to the
5 invention, characterized by the following steps:

- (a) administering an effective amount of the peptide according to the invention to an animal; and
- (b) isolating the antibody produced by the animal in response to the administration of step (a) from the animal.

10

Another subject of the invention relates to a method for producing an antibody according to the invention, characterized by the following steps:

- (a) contacting a B cell with an effective amount of the peptide according to the invention;
- 15 (b) fusing the B cell of step (a) with a myeloma cell to obtain a hybridoma cell; and
- (c) isolating the antibody produced by the cultivated hybridoma cell.

More particularly, the antibody may be produced by initiating an immune response in a non-human animal by administrating a peptide of the invention to an animal, removing an
20 antibody containing body fluid from said animal, and producing the antibody by subjecting said antibody containing body fluid to further purification steps. Alternatively, the antibody may be produced by initiating an immune response in a non-human animal by administrating an antigen, fragment or variant thereof, as defined in the present invention, to said animal, removing the spleen or spleen cells from said animal and/or producing
25 hybridoma cells of said spleen or spleen cells, selecting and cloning hybridoma cells specific for said antigen, fragment or variant thereof and producing the antibody by cultivation of said cloned hybridoma cells.

In a preferred embodiment the antibody produced according to a method of the invention is
30 additionally purified. Methods of purification are known to the skilled artisan.

The antibody may be used in methods for preventing or treating an infection. Accordingly, still another subject of the invention relates to a pharmaceutical composition, especially a

- vaccine, comprising an antibody of the invention. The pharmaceutical composition may encompass further components as detailed above. The composition may further encompass substances increasing their capacity to stimulate T cells. These include T helper cell epitopes, lipids or liposomes or preferred modifications as described in WO01/78767.
- 5 Another way to increase the T cell stimulating capacity of epitopes is their formulation with immune stimulating substances for instance cytokines or chemokines like interleukin-2, -7, -12, -18, class I and II interferons (IFN), especially IFN-gamma, GM-CSF, TNF-alpha, flt3-ligand and others.
- 10 A further subject of the invention relates to a pharmaceutical composition comprising the pharmaceutical peptide of the invention or the pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof for the immunization of a subject against an infection or the treatment of a subject having an infection, wherein the infection is preferably a *S. pyogenes* infection. In another aspect of the invention a pharmaceutical peptide of the invention or a pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof is used for the manufacture of a medicament for the immunization of a subject against an infection or the treatment of a subject having an infection, wherein the infection is preferably a *S. pyogenes* infection, more preferably an infection with *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61; M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Alternatively, a pharmaceutical peptide or a pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof is used in a method of immunizing or treating a subject in need thereof, wherein an effective amount of the pharmaceutical peptide or the pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof is administered to the subject. The subject may be immunized in order to prevent an infection, particularly a *S. pyogenes* infection, or may be treated to ameliorate or cure an infection, particularly a *S. pyogenes* infection. The determination of the effective amount to be administered is within the knowledge of the skilled practitioner. Exemplary amounts are mentioned below.
- 25
- 30

The pharmaceutical peptides or the pharmaceutical nucleic acids of the invention are generally useful for inducing an immune response in a subject. The vaccine used for

immunization may be administered to a subject susceptible to infection by *S. pyogenes*, preferably mammals, and still more preferably humans. Potential modes of administration include oral, intranasal, intramuscular, intra-lymph node, intradermal, intraperitoneal, subcutaneous, and combinations thereof, but most preferably intramuscular injection. The 5 volume of the dose for intramuscular administration is preferably up to about 5 mL, for example, between 0.3 mL and 3 mL, between 1 mL and 3 mL, about 0.5 to 1 mL, or about 2 mL. The amount of protein comprising the antigen in each dose should be enough to confer effective immunity to decrease the risk of developing clinical signs, e.g. resulting from *S. pyogenes* infection. In different embodiments, the unit dose of protein should be up 10 to about 5 µg protein/kg body weight, between about 0.2 to 3 µg, between about 0.3 to 1.5 µg, between about 0.4 to 0.8 µg, or about 0.6 µg. In alternative embodiments unit doses of protein could be up to about 6 µg protein/kg body weight, between about 0.05 to 5 µg, or between about 0.1 to 4 µg. In different embodiments, the dose is administered 1 to 3 times, e.g. with an interval of 1 to 3 weeks. Representative amounts of protein per dose are from 15 approximately 1 µg to approximately 1 mg, more preferably from approximately 5 µg to approximately 500 µg, still more preferably from approximately 10 µg to approximately 250 µg and most preferably from approximately 25 µg to approximately 100 µg.

In still another aspect of the invention the antibody of the invention or functional fragment 20 thereof is used for the manufacture of a medicament for the treatment of an infection, preferably a *S. pyogenes* infection, more preferably an infection with *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Alternatively, the antibody of the invention is used in a method of treating a subject 25 in need thereof, wherein an effective amount of the antibody of the invention is administered to the subject. The subject may be treated to ameliorate or cure an infection, particularly a *S. pyogenes* infection. The determination of the effective amount to be administered is within the knowledge of the skilled practitioner.

30 The treatment involves administering an effective amount of an antibody of the invention to a subject, preferably a mammal, more preferably a human. Thus, antibodies against the antigens, fragments or variants thereof of the present invention may be employed to inhibit and/or treat infections, particularly bacterial infections and especially infections arising

from *S. pyogenes*, especially *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370.

- 5 An “effective amount” of a pharmaceutical peptide, a pharmaceutical nucleic acid or an antibody of the invention may be calculated as that amount capable of exhibiting an *in vivo* effect, e.g. preventing or ameliorating a sign or symptom of infection, particularly *S. pyogenes* infection, especially of *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Such amounts may be determined by one of skill in the art. Preferably, such a composition is administered parenterally, preferably intramuscularly or subcutaneously. However, it may also be formulated to be administered by any other suitable route, including orally or topically. The selection of the route of delivery and dosage of such therapeutic compositions is 15 within the skill of the art.

Treatment in the context of the present invention refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include 20 those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

Another subject of the invention relates to a method of diagnosing a *S. pyogenes* infection comprising the steps of:

- 25 (a) contacting a sample obtained from a subject with the peptide according to the invention; and
(b) detecting the presence of an antibody against *S. pyogenes* in the sample.

The peptides of the invention may be used for the detection of the *S. pyogenes*, particularly 30 *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Preferably such detection is for diagnosis, more preferable for the diagnosis of a disease, most preferably for the diagnosis of a *S. pyogenes* infection. The

peptides or polypeptides may be used to detect the presence of a *S. pyogenes*-specific antibody or fragment thereof e.g. in a sample obtained from a subject. The sample may be e.g. a blood sample. Alternatively, the presence of a *S. pyogenes*-specific antigen can be detected using an antibody of the invention.

5

Accordingly, an alternative method of diagnosing a *S. pyogenes* infection comprises the steps of:

- (a) contacting a sample obtained from a subject with the antibody according to the invention; and
- 10 (b) detecting the presence of an antigen of *S. pyogenes* in the sample.

The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of the peptides or antibodies of the present invention in cells and tissues or body fluids, including determination of normal and abnormal levels. Assay

15 techniques that can be used to determine levels of a peptide or an antibody, in a sample derived from a host are well known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Among these, ELISAs frequently are preferred. An ELISA assay initially comprises preparing an antibody specific to the peptide, particularly the antigen, preferably a
20 monoclonal antibody. In addition, a reporter antibody generally is prepared which binds to the monoclonal antibody. The reporter antibody is attached to a detectable reagent such as radioactive, fluorescent or enzymatic reagent, such as horseradish peroxidase enzyme.

The peptides or antibodies of the present invention may also be used for the purpose of or
25 in connection with an array. More particularly, at least one of the peptides or antibodies of the present invention may be immobilized on a support. Said support typically comprises a variety of antigens and fragments thereof whereby the variety may be created by using one or several of the peptides or antibodies of the present invention. The characterizing feature of such array as well as of any array in general is the fact that at a distinct or predefined

30 region or position on said support or a surface thereof, a distinct polypeptide is immobilized. Because of this any activity at a distinct position or region of an array can be correlated with a specific polypeptide. The number of different peptides or antibodies of

the present invention immobilized on a support may range from as little as 10 to several 1000 different peptides or antibodies of the present invention.

The manufacture of such arrays is known to the one skilled in the art and, for example, 5 described in US patent 5,744,309. The array preferably comprises a planar, porous or non-porous solid support having at least a first surface. Preferred support materials are, among others, glass or cellulose. It is also within the present invention that the array is used for any of the diagnostic applications described herein. Apart from the peptides or antibodies of the present invention also the nucleic acid molecules according to the present invention 10 may be used for the generation of an array as described above.

Another aspect of the invention relates to a method for identifying a ligand capable of binding to a peptide according to the invention comprising:

- (a) providing a test system comprising the peptide,
- 15 (b) contacting the test system with a test compound, and
- (c) detecting a signal generated in response to the binding of the test compound to the peptide.

More particularly, the method may be carried out by contacting an isolated or immobilized 20 peptide according to the invention with a candidate ligand under conditions to permit binding of the candidate ligand to the peptide, wherein the test system comprises a component capable of providing a detectable signal in response to the binding of the candidate ligand to said peptide; and detecting the presence or absence of a signal generated in response to the binding of the ligand to the peptide. The ligand may be an 25 agonist or an antagonist.

Test systems for detection binding of a ligand are known to the skilled artisan and include e.g. binding assays with labeled ligand such as radioligands, fluorescence-labeled ligands or enzymic-labeled ligands.

30 The test compound can be any test compound either naturally occurring or chemically synthesized. Naturally occurring test compounds include in particular antibodies, preferably those showing similarity to the antibodies of the invention. In one preferred

embodiment of the invention the test compound is provided in the form of a chemical compound library. Chemical compound libraries include a plurality of chemical compounds and have been assembled from any of multiple sources, including chemically synthesized molecules and natural products, or have been generated by combinatorial chemistry techniques. They are especially suitable for high throughput screening. They may be comprised of chemical compounds of a particular structure or compounds of a particular creature such as a plant.

The method for identifying a ligand may also include the following steps:

- 10 (a) providing a peptide according to the invention,
- (b) providing an interaction partner to the peptide especially an antibody according to the invention,
- (c) allowing interaction of the peptide to said interaction partner to form a interaction complex,
- 15 (d) providing a test compound,
- (e) allowing a competition reaction to occur between the test compound and the interaction complex, and
- (f) determining whether the test compound inhibits or reduces the interaction activities of the peptide with the interaction partner.

20 The ligands identified may be employed, for instance, to inhibit diseases arising from infection with Streptococcus, especially *S. pyogenes* and may therefore be formulated in a pharmaceutical composition.

25 In a last aspect, the peptide according to the invention is used for the isolation and/or purification and/or identification of a ligand of the peptide, wherein the isolation and/or purification and/or identification of the ligand may be carried out as detailed above or as known to the person skilled in the art. In a preferred embodiment of the invention an affinity device may be used. The affinity device may comprise at least a support material
30 and any peptide according to the present invention, which is attached to the support material. Because of the specificity of the peptides according to the present invention for their target cells or target molecules or their interaction partners, the peptides allow a selective removal of their interaction partner(s) from any kind of sample applied to the

support material provided that the conditions for binding are met. The sample may be a biological or medical sample, including but not limited to, fermentation broth, cell debris, cell preparation, tissue preparation, organ preparation, blood, urine, lymph liquid, liquor and the like. The peptide may be attached to the matrix in a covalent or non-covalent manner. Suitable support material is known to the one skilled in the art and can be selected from the group comprising cellulose, silicon, glass, aluminium, paramagnetic beads, starch and dextrane.

The present invention is further illustrated by the following figures, examples and the sequence data, from which further features, embodiments and advantages may be taken. It is to be understood that the present examples are given by way of illustration only and not by way of limitation of the disclosure.

Figure 1 shows the protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model.

Figure 2 shows the protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model.

Figure 3 shows the protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model.

Figure 4 shows the protection achieved by active immunization with selected *S. pyogenes* antigens in a mouse lethality model.

Table 1 shows the recombinant proteins of *S. pyogenes* and fragments thereof assessed for protection in murine models of infection.

Table 2 shows the oligonucleotides used for the cloning of genes encoding antigenic proteins and fragments thereof of *S. pyogenes*.

Table 3 shows the *S. pyogenes* strains used for the gene conservation study.

Table 4 shows the oligonucleotides used for PCR and sequencing of the *S. pyogenes* genes.

Table 5 shows the variable amino acid positions of Spy0269 from *S. pyogenes* strains.

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Table 6 shows the variable amino acid positions of Spy0292 from *S. pyogenes* strains.

Table 7 shows the variable amino acid positions of Spy0416 from *S. pyogenes* strains.

10 Table 8 shows the variable amino acid positions of Spy0488 from *S. pyogenes* strains.

Table 9 shows the variable amino acid positions of Spy0872 from *S. pyogenes* strains.

Table 10 shows the variable amino acid positions of Spy0895 from *S. pyogenes* strains.

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Table 11 shows the variable amino acid positions of Spy1536 from *S. pyogenes* strains.

Table 12 shows the variable amino acid positions of Spy1666 from *S. pyogenes* strains.

20

FIGURES

Figure 1: Protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model. CD-1 mice (10 mice per group)

25 were immunized subcutaneously with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged with the MA-A20 (emm type 23) strain. Survival was monitored for 14 days post-challenge. Mice were immunized subcutaneously with 50 µg recombinant protein adjuvanted with CFA/IFA. (A) Spy0292, and its sub-constructs Spy0292-1 and Spy0292-3; (B) Spy0872 and its sub-construct Spy0872-2.
30 Anesthetized mice were challenged intranasally with 10⁸ cfu *S. pyogenes* MA-A20. Adjuvant control mice were used as negative controls, while M1 (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

Figure 2: Protection achieved by active immunization with selected *S. pyogenes* antigens and sub-contracts in a mouse lethality model. CD-1 mice (10 mice per group) were immunized subcutaneously with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged with the MA-A20 (emm type 23) strain. Survival was monitored for 14 days post-challenge. Mice were immunized subcutaneously with 50 µg recombinant protein adjuvanted with CFA/IFA. (A) Spy0269 and its sub-construct Spy0269-1; (B) Spy0416A and 3 sub-constructs (Spy0416A-1, Spy0416A-6 and Spy0416A-7) and Spy0416B. Anesthetized mice were challenged intranasally with 10^8 cfu *S. pyogenes* MA-A20. Adjuvant control mice were used as negative controls, while M1 protein (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

Figure 3: Protection achieved by active immunization with selected *S. pyogenes* antigens or sub-contracts in a mouse lethality model. CD-1 mice (10 mice per group) were immunized subcutaneously with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged with the MA-A20 (emm type 23) strain. Survival was monitored for 14 days post-challenge. Mice were immunized subcutaneously with 50 µg recombinant protein adjuvanted with aluminum hydroxide. (A) Spy1727, Spy0269-1, Spy0872-2, and Spy0416A-1; (B) Spy1666, Spy1536, Spy0895, and Spy0292-1. Anesthetized mice were challenged intranasally with 10^8 cfu *S. pyogenes* MA-A20. Adjuvant control mice were used as negative controls, while M1 protein (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

Figure 4: Protection achieved by active immunization with selected *S. pyogenes* antigens in a mouse lethality model. BALB/c mice (10 mice per group) were immunized intranasally with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged either with (A) MA-A20 (emm type 23) strain or with (B) MA-A147 (emm type 11/106) strain. Survival was monitored for 14 days post-challenge. Mice were immunized intranasally with 30-50 µg recombinant protein adjuvanted with IC31TM. (A) Spy1536 and Spy0895; (B) Spy1727 and Spy1536. Anesthetized mice were challenged intranasally with 10^6 cfu *S. pyogenes* MA-A20 or 10^8 cfu *S. pyogenes* MA-A147. Adjuvant control mice were used as negative controls, while M1 protein (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

EXAMPLES

Example 1: Group A streptococcal antigens and fragments thereof inducing protective immune responses against lethal sepsis in intranasal challenge models.

5

Experimental procedures

Cloning and expression of recombinant pneumococcal proteins

10 Cloning of genes / DNA fragments:

The gene/DNA fragment of interest (see Table 1) was amplified from genomic DNA of *Streptococcus pyogenes* SF370 (serotype M1) by PCR using gene specific primers (see Table 2). Apart from the gene specific part, the primers had restriction sites that aided in a directional cloning of the amplified PCR product. The gene annealing (specific) part of the 15 primer ranged between 15-30 bases in length. The PCR products obtained were digested with the appropriate restriction enzymes and cloned into the pET28b (+) vector (Novagen) for His-tagged proteins. The constructs including full length and fragments of the selected antigens are listed in Table 1. Once the recombinant plasmid was confirmed to contain the gene of interest, *E. coli* BL21 star[®] cells (Invitrogen) that served as expression host were 20 transformed.

Expression and purification of proteins:

E. coli BL21 star[®] cells harboring the recombinant plasmid were grown into log phase in the required culture volume. Once an OD_{600nm} of 0.6 was reached the culture was induced 25 with 0.5 mM IPTG (isopropyl-beta-D-thiogalactopyranoside) at 37°C for 3 hours. The cells were harvested by centrifugation, lysed by a combination of the freeze-thaw method followed by disruption of cells with BugBuster[®] (Novagen). The lysate was separated by centrifugation into soluble (supernatant) and insoluble (pellet) fractions. Depending on the location of the protein different purification strategies were applied.

30

A) If the His-tagged protein was in the soluble fraction, protein purification was done by binding the supernatant to Ni-Sepharose beads (Ni-Sepharose™ 6 Fast Flow, GE Healthcare). Due to the presence of the hexa Histidine (6xHIS) at the C terminus of the

expressed protein, it bound to the Ni-Sepharose while the other contaminating proteins were washed from the column by wash buffer. The protein was eluted by 500 mM Imidazole in 20 mM NaH₂PO₄, 0.5 mM NaCl buffer at pH 7.4. The eluate was concentrated, assayed by Bradford for protein concentration and checked by SDS-PAGE
5 and Western blot.

B) If the protein was present in the insoluble fraction the pellet was solubilized in suitable buffer containing 8 M urea and applied onto the Ni-NTA column under denaturing conditions (in buffer containing 8 M urea) using the same materials and procedure as
10 mentioned above. Contaminating proteins were washed from the column by wash buffer without urea. Refolding of the His-tagged protein was performed while the protein was immobilized on the Ni-NTA matrix. After renaturation, proteins were eluted by the addition of 500 mM Imidazole. The eluate was dialyzed to remove traces of urea and concentrated if the volume was large, checked by SDS-PAGE and measured by the
15 Bradford method.

Animal protection studies

Animals:

20 CD-1 or BALB/c female mice (6 – 8 weeks) were used.

Active immunization (subcutaneous route):

50 µg of recombinant proteins buffered in PBS were injected subcutaneously into CD-1 mice (volume 100 µL), adjuvanted with Complete Freund adjuvant (CFA, final
25 concentration: 50%), aluminium hydroxide (ALUM, final concentration: 1%) or IC31TM (final concentration: 100 nmol L-KLKLLLLKLK (SEQ ID NO: 55), 4 nmol oligodeoxynucleotide ODN1a (dIdC)₁₃ in PBS) (Intercell AG, Vienna, Austria). Animals were boosted twice with the same amount of protein and adjuvant (except for CFA where Incomplete Freund adjuvant (IFA) was used for the booster immunizations; final
30 concentration: 50%), at days 14 and 28. The published (Dale et al., J. Immunol. 151: 2188 (1993)) protective M1 or M23 protein antigens were used as positive controls, while mice immunized with adjuvant only served as negative controls. Antibody titers were measured at day 35 by ELISA using the respective recombinant proteins.

Active immunization (intranasal route):

30 - 50 µg of recombinant proteins buffered in PBS were injected intranasally into BALB/c mice (volume 20 µL), adjuvanted with IC31™ (final concentration: 10 nmol L-
5 KLKLLLLLK (SEQ ID NO: 55), 0.4 nmol oligodexoxynucleotide ODN1a (dIdC)13 in PBS) (Intercell AG, Vienna, Austria). Animals were boosted three times with the same amount of protein and adjuvant at days 7, 14 and 28. The published protective M1 or M23 protein antigens were used as positive controls, while mice immunized with adjuvant only served as negative controls. Antibody titers were measured at day 35 by ELISA using the
10 respective recombinant proteins.

Bacterial challenge:

Freshly grown *S. pyogenes* strains MA-A20 or MA-A147 were used. 1 mL bacterial suspension from an o/n culture of the respective *S. pyogenes* strain was added to 50 mL
15 THY culture medium. Optical density was measured until the bacterial suspension reached an OD_{600nm} between 0.4 and 0.6. Bacterial counts were determined using an individually established growth curve. Bacterial cells were spun down and adjusted with PBS to obtain the desired cfu count. In order to determine the viable cell numbers present in the bacterial inoculum, cfus were determined via plating on blood agar plates. 10⁶ - 10⁸ cfus were
20 applied intranasally (20 µL) into individually anesthetized mice. Protection by immunization was measured by a bacteraemia / sepsis model where survival rates were followed for 2 to 3 weeks post-challenge and survival was expressed in percentage of the total number of animals (10 mice / group).

25 ***Results***

Group A streptococcal antigens and/or their fragments were identified showing protection in an intranasal mouse sepsis/lethality model. As the target indication for a preventive vaccine in humans is pharyngitis, an intranasal challenge model for the evaluation of
30 candidate antigens is believed to be physiologically more relevant than an intravenous or intraperitoneal model, which have been described previously (Guzman et al., J. Inf. Dis. 179: 901 (1999); Stalhammar-Carlemalm et al., Mol. Microbiol. 33: 208 (1999)). Therefore protection was assessed in three distinct models, all applying the bacterial

challenge via the intranasal route. Protection was observed for 9 distinct proteins in the intranasal challenge model, some of which were tested as a fragment of the full length recombinant protein.

- 5 Since protection against streptococcal challenge is mediated by antibodies, immunizations were first performed using CFA/IFA as adjuvant in order to obtain very high levels of antibodies. Subsequently, experiments were also performed with Alum and IC31™ as adjuvants, as these adjuvants are suited for use in humans and would be a preferred choice for a vaccine to prevent group A streptococcal infections in humans. As can be seen for the
10 experiment depicted in Figure 1, fragment Spy0292-1 performed as well as full length Spy0292 protein for protection, while Spy0292-3 showed lower levels of protection. This clearly indicates that one region useful for protection lies within the sequence encompassing the Spy0292-1 protein.
- 15 Similar results were obtained for the proteins, Spy0269 (good protection also observed with Spy0269-1), Spy0416 (good protection also observed with Spy0416A-1, Spy0416A-6 and Spy0416A-7), and Spy0872 (good protection also observed with Spy0872-2).

For the proteins Spy0488, Spy0895, and Spy1727 full length recombinant proteins were
20 used (Table 1), as these proteins have been shown for the first time to be capable to provide protection against lethal *S. pyogenes* challenge. Especially protein Spy0895 shows promise as a vaccine candidate, because it provided protection against group A streptococcal infection in all three models listed in Table 1.

- 25 Spy1536 and Spy1666 have been shown to provide protection in an intravenous challenge model before (WO 2004/078907), but importantly it could now be shown that they also provide protection in the physiologically more relevant intranasal challenge model. Spy1536 was most consistent in providing significant protection in all three models of GAS infection. Besides these two antigens, Spy0895 and Spy1536, several antigens
30 showed protection in at least 2 models: Spy0269-1, Spy0292-1, Spy0416A-1, Spy0872-2, Spy1666 and Spy1727. Importantly, several antigens showed a level of protection that was as high as the level seen for the positive control protein M1 (e.g. Spy0416A-1, Spy0488, Spy0895; Table 1).

These data clearly provide evidence, that the selected proteins are promising candidates for vaccine development. In addition, proteins Spy0269, Spy0292, Spy0416, and Spy0872 have been shown to possess amino acid sequences that are dispensable for protection, since 5 sub-fragments were capable to provide the same or even superior levels of protection than the full length recombinant protein.

Table 1: Recombinant proteins of *S. pyogenes* and fragments thereof assessed for protection in murine models of infection.

10

ORF/ Protein	Length ¹ (aa)	Amino acids ¹ (from - to)	SEQ ID No	Calculated MW (kDa) ²	Vector	Base pairs ¹ (from - to)	Protection ³
Spy0269	837	36 - 873	57	92.34	pET28b	106-2619	10% (30%, 60%) ^A
Spy0269-1	452	37-488	1	50.85	pET28b	109-1464	50% (10%, 50%) ^{B,C}
Spy0292	388	23 - 410	68	44.91	pET28b	67-1233	60% (10%, 80%) ^C
Spy0292-1	162	23-184	2	19.41	pET28b	67-554	56% (10%, 90%) ^{A,B}
Spy0292-3	278	23-300	3	32.39	pET28b	67-900	30% (10%, 90%) ^A
Spy0416A	834	34 - 867	89	95.80	pET28b	100-2601	20% (10%, 63%) ^A
Spy0416A-1	644	34-677	4	74.70	pET28b	100-2031	80% (20%, 80%) ^{C,A}
Spy0416A-6	311	148-458	5	38.77	pET28b	442-1374	40% (10%, 63%) ^A
Spy0416A-7	487	72-558	6	57.68	pET28b	214-1674	63% (10%, 63%) ^A
Spy0416B	882	736 - 1617	56	103.08	pET28b	2206-4851	20% (10%, 63%) ^A
Spy0488	331	1-331	8	37.84	pET28b	1-993	90% (20%, 80%) ^{C,A}
Spy0872	613	28 - 640	120	68.38	pET28b	82-1920	20% (0%, 60%) ^A
Spy0872-2	290	351-640	7	33.02	pET28b	1051-1920	60% (0%, 60%) ^{A,C,B}
Spy0895	261	2-262	9	32.15	pET28b	4-786	90% (20%, 80%) ^{C,A,B}
Spy1536	314	32-345	131	35.27	pET28b	94-1035	70% (20%, 80%) ^{C,B}
Spy1666	315	23-337	132	37.02	pET28b	67-1011	60% (20%, 80%) ^{C,B}
Spy1727	263	1-263	10	32.43	pET28b	1-789	70% (20%, 80%) ^{C,B}

¹ Length, amino acids and base pairs are calculated for the *S. pyogenes* gene specific sequence only.

² The calculated molecular weight includes amino acids derived from the vector and the His6-tag.

³ Protection is based on the animal model as indicated:

A s.c. immunization using CFA/IFA as adjuvant, i.n. challenge with *S. pyogenes* A20

B s.c. immunization using ALUM as adjuvant and i.n. challenge with *S. pyogenes* A20

C intranasal immunization using IC31™ or a mucosal adjuvant and intranasal challenge with either *S. pyogenes* A20 or A147.

15 Brackets show protection in the respective model with the negative (PBS + adjuvant only) and positive control (M protein). If protection was seen in more than one model, the protection data of the model listed first are shown.

20

Table 2: Oligonucleotides used for the cloning of genes encoding antigenic proteins and fragments thereof of *S. pyogenes*.

ORF-protein	Plasmid name	Primer ¹	Name	Restriction enzyme
SPy0269	pET28b-SPy0269	TAGTAGCCATGGGGCATGATGATAGGCCCTA GGA SEQ ID NO: 21	210-2129	Ncol
		TAGTAGGCCGCCTTGTAGATTCCTAGG GAACT SEQ ID NO: 22	210-2196	NotI
SPy0269-1	pET28b-SPy0269-1	TAGTAGCCATGGGGCATGATGATAGGCCCTA GGA SEQ ID NO: 23	210-2129	Ncol
		TAGTAGGCCGCACAGGGCATTAGG G SEQ ID NO: 24	210-2719	NotI
SPy0292	pET28b-SPy0292	TAGTAGCCATGGGGCAAGAGTATTGGTA ACTGC SEQ ID NO: 25	210-2131	Ncol
		TAGTAGGCCGCCTAAAGAGGTATTGAC ATACCT SEQ ID NO: 26	210-2197	NotI
SPy0292-1	pET28b-SPy0292-1	TAGTAGCCATGGGGCAAGAGTATTGGTA ACTGC SEQ ID NO: 27	210-2131	Ncol
		TAGTAGGCCGCCTAAACAAATTTTC ATCATC SEQ ID NO: 28	210-2954	NotI
SPy0292-3	pET28b-SPy0292-3	TAGTAGCCATGGGGCAAGAGTATTGGTA ACTGC SEQ ID NO: 29	210-2131	Ncol
		TAGTAGGCCGCCTTCATTAACTGGAC TTTTTG SEQ ID NO: 30	210-2956	NotI
SPy0416A	pET28b-SPy0416A	TAGTAGGAATTGGCAGATGAGCTAACGCA CAATG SEQ ID NO: 31	210-2246	EcoRI
		TAATGCTCGAGCTCTGAACCAAGAGTGA CAAG SEQ ID NO: 32	210-2247	Xhol
SPy0416A-1	pET28b-SPy0416A-1	TAGTAGGAATTGGCAGATGAGCTAACGCA CAATG SEQ ID NO: 33	210-2246	EcoRI
		TAGTAGCTCGAGTGGCCCTTGTGACGGC GTG SEQ ID NO: 34	210-2663	Xhol
SPy0416A-6	pET28b-SPy0416A-6	TAGTAGGAATTGGCAGTATTGACACAGG G SEQ ID NO: 35	210-2715	EcoRI
		TAGTAGCTCGAGTAGGCTATCTTTATGTC SEQ ID NO: 36	210-2717	Xhol
SPy0416A-7	pET28b-SPy0416A-7	TAGTAGGAATTGGTACAACACTCTCAA G SEQ ID NO: 37	210-2716	EcoRI
		TAGTAGCTCGAGACTCTCTGTACCATGCC SEQ ID NO: 38	210-2718	Xhol
SPy0416B	pET28b-SPy0416B	TAGTAGGAATTGGTACATGAGACCCACAAA AGGGC SEQ ID NO: 39	210-2248	EcoRI
		TAGTAGCTCGAGCGGTGATGGTAGGGCTT TGC SEQ ID NO: 40	210-2249	Xhol
SPy0488	pET28b-SPy0488	TAGTAGCCATGGGCTTGGCGCAGATTAG TCCATT SEQ ID NO: 41	210-2139	Ncol
		TAGTAGGCCGCCTGTATTGGAAAGAGT GGAAC SEQ ID NO: 42	210-2199	NotI
SPy0872	pET28b-SPy0872	TAGTAGCCATGGGGCATGAACTTGTG CAATT SEQ ID NO: 43	210-2143	Ncol
		TAGTAGGCCGCCTGTATTGGAAAGAGT GGAAC SEQ ID NO: 44	210-2144	NotI
SPy0872-2	pET28b-SPy0872-2	TAGTAGCCATGGGGCGCTATAAAATCATG CT SEQ ID NO: 45	210-2962	Ncol
		TAGTAGGCCGCCTGTATTGGAAAGAGT GGAAC SEQ ID NO: 46	210-2144	NotI
SPy0895	pET28b-SPy0895	TAGTAGCCATGGGCACATAATAATCAAACA	210-2145	Ncol

ORF-protein	Plasmid name	Primer ¹	Name	Restriction enzyme
		CTA SEQ ID NO: 47 <u>TAGTAGGCCGCCGCGACAATAGATGTCT</u> CCAAG SEQ ID NO: 48	210-2201	NotI
SPy1536	pET28b-SPy1536	TAGTACCCATGGGCATTGAAATGCCCTGGA GGCG SEQ ID NO: 49 TAGTAGGCCGCCGCTTCGAAAGATAAAC CACTGC SEQ ID NO: 50	210-2161	NcoI
			210-2207	NotI
SPy1666	pET28b-SPy1666	TAGTAGCCATGGGCACAAAAGAACATTTCATC ACCTG SEQ ID NO: 51 TAGTAGGCCGCCGCTTCGAAATTTTTG GCAAC SEQ ID NO: 52	210-2165	NcoI
			210-2209	NotI
SPy1727	pET28b-SPy1727	TAGTAGCCATGGGCGTGAACACGACGGAA CAAG SEQ ID NO: 53 TAGTAGGCCGCCGCTTCCTTCTAAATATT TCTCT SEQ ID NO: 54	210-2167	NcoI
			210-2210	NotI

¹ Primer, letters in bold indicate gene-specific sequences, letters underlined indicate the restriction enzyme sites, letters in normal font indicate sequences necessary for cloning, but not present in the final plasmid construct used for expression. The first primer always refers to the sense and the second primer to the anti-sense oligonucleotide in relation to the encoded gene used for amplification.

5

Example 2: Group A streptococcal antigens and variants thereof.

10 Experimental procedures

Preparation of streptococcal genomic DNA

5 mL Todd-Hewitt Broth medium were inoculated with the respective strain of *S. pyogenes* (as listed in Table 3) from a frozen stab and grown without shaking at 37°C overnight. 4 mL of the culture were then harvested by centrifuging at 13,000 rpm in a biofuge fresco (HaerCUS) for 5 min and the supernatant was removed. DNA was isolated from the bacterial cell pellets following the protocol of Wizard® Genomic DNA Purification Kit (Promega). The DNA pellets were finally dried on air and dissolved in 70 µl ddH₂O.

15

PCR and sequence analyses of *S. pyogenes* genes

20 In order to determine the sequence of an antigen from diverse *S. pyogenes* strains, PCR was performed with primers specific for the gene of interest. *S. pyogenes* strains used for these analyses are shown in Table 3. Oligonucleotide sequences as primers for PCR were designed for the selected antigens in order to be able to amplify the full gene. Sequencing was performed with dedicated primers using the PCR products as templates. The sequences of the oligonucleotides are listed in Table 4. Genomic DNA of all *S. pyogenes* sequences of the oligonucleotides are listed in Table 4. Genomic DNA of all *S. pyogenes*

25

strains was prepared as described above. PCR was performed in a reaction volume of 25 µl using Taq polymerase (1 U), 200 nM dNTPs, 10 pMol of each oligonucleotide and the kit according to the manufacturer's instructions (Invitrogen, The Netherlands). As standard, 30 cycles (1x: 5 min. 95°C, 30x: 30 sec. 95°C, 30 sec. 56°C, 120 sec. 72°C, 1x 4 min. 5 72°C) were performed, unless conditions had to be adapted for individual primer pairs. PCR samples were sequenced with the oligonucleotides as listed in Table 10. Sequencing was performed at Agowa (Germany).

Table 3: *S. pyogenes* clinical isolates utilized for the present study.

No.	Strain	Country of origin	Serotype
1	Schmitz 1/94	Netherlands	1
2	Schmitz 1/12	Portugal	1
3	Schmitz 1/5	Portugal	1
4	Schmitz 2/14	Germany	1
5	Schmitz 1/74	England	3
6	Schmitz 1/35	Spain	3
7	Schmitz 1/41	France	3
8	RDN 78	unknown	3.1
9	Schmitz 1/17	Portugal	4
10	Schmitz 1/156	Switzerland	4
11	Schmitz 1/22	Spain	4
12	RDN 60	unknown	5
13	Schmitz 1/174	Austria	6
14	Schmitz 1/97	Belgium	6
15	Schmitz 1/29	Spain	9
16	Schmitz 1/92	Netherlands	11
17	Schmitz 1/39	Spain	12
18	Schmitz 1/248	Poland	12
19	Schmitz 1/59	England	12
20	RDN 02	unknown	19
21	Schmitz 1/76	England	22
22	Schmitz 1/177	Austria	22
23	Schmitz 1/43	France	22
24	Schmitz 2/32	Germany	22
25	RDN 136	unknown	22.2
26	Schmitz 1/136	Germany	25
27	Schmitz 1/56	France	28
28	Schmitz 1/108	Belgium	28
29	Schmitz 1/85	Netherlands	28
30	Schmitz 2/50	Germany	28
31	Schmitz 1/194	Italy	44
32	Schmitz 1/234	Turkey	44
33	Schmitz 1/103	Belgium	44
34	Schmitz 1/253	Poland	49
35	Schmitz 1/141	Germany	49
36	Schmitz 1/123	Germany	49

37	Schmitz 2/30	Germany	66 or 90
38	Schmitz 1/144	Germany	76
39	Schmitz 1/99	Belgium	78
40	RDN 120	unknown	81
41	Schmitz 1/142	Germany	83
42	Schmitz 1/176	Austria	83
43	Schmitz 1/25	Spain	83
44	RDN 75	unknown	85
45	Schmitz 2/46	Germany	89
46	Schmitz 2/9	Germany	90
47	Schmitz 2/23	Germany	90
48	RDN 116	unknown	94
49	Schmitz 1/55	France	118
50	Schmitz 1/68	England	118
51	Schmitz 1/3	Portugal	118

Table 4: Oligonucleotides used for sequence conservation analyses. Shown are the ORF and primer names, orientation of the primer relative to the gene, the sequence, and the position relative to the gene. Oligonucleotides were used for both PCR amplification of the gene or gene fragment and subsequent sequence analyses.

ORF	Primer name	Orientation	Sequence	SEQ ID NO:	Position relative to gene
Spy0269	210-4752	sense	TGACCTTCAAATCATTGCTGA	209	-103 to -82
	210-4759	antisense	TTTTGCACCTCTGGTGTCAA	210	104 to 1034
	210-4754	sense	TTGCCAAAGCTAGTCAGGT	211	931 to 951
	210-4761	antisense	AGTATTATCAATCGGCTCACG	212	2028 to 2049
	210-4756	sense	AAAAGCTCATTTGCAATATCTAAGG	213	1967 to 1992
	210-4763	antisense	GCTGGTGAATCTGATTTTCAA	214	2875 to 2897
Spy0292	210-4575	sense	TCTTGTGAGGTAAGTCATTACCTTAG	215	-79 to -53
	210-4576	antisense	TTCATCATCTGGTCTGTATTAGG	216	516 to 540
	210-4577	sense	GGTCGTCATTCACAATGCG	217	464 to 483
	210-4578	antisense	GCGATCATTTGCGATGATTTC	218	1031 to 1052
	210-4579	sense	AAACTGTCAAACCTGTAGCCC	219	946 to 967
	210-4580	antisense	TGTTAGGATTGGCCTAGTTG	220	1304 to 1325
Spy0416	210-4588	sense	TGAGTTAAATGATTAACATTAAACTGGT	221	-56 to -29
	210-4591	antisense	TGACATATAAGCAATTGATGCG	222	1387 to 1408
	210-4592	sense	CCATCTATTCAAGCTGTGCGAC	223	1327 to 1350
	210-4595	antisense	CTTGTGTCACTAGCAGTGGTAGAC	224	2802 to 2824
	210-4596	sense	TTGCAGCCTTCAAAGGTG	225	2749 to 2767
	210-4599	antisense	AAGACACATTACCAAGCTCTATCTC	226	4128 to 4153
	210-4600	sense	CAGATGGTTCTAACCAATTTC	227	4063 to 4085
	210-4603	antisense	AATCTCAAAGAAAGGTGAGACTG	228	4982 to 5005
Spy0488	210-5497	sense	AAAGCTCGTCAATTATATGATT	229	-195 to -171
	210-4767	antisense	TTAAATGAGAGTTGTCATTGTTCA	230	497 to 522
	210-4765	sense	TTTCCTGTTCAACCCGAAG	231	404 to 424
	210-4766	antisense	GCCCTCACAGCTACTTCAGA	232	1052 to 1072
Spy0872	210-4581	sense	CAAAATCATAGTAAACCTGATCTAACG	233	-55 to -26
	210-4584	antisense	GAAGAAATTAGTTGCGATTCGG	234	1103 to 1124
	210-4585	sense	GTTGCTGTAGCACCAAGGTATC	235	1005 to 1026

	210-4587	antisense	CCAGCACGAATTAGATCATCTAG	236	2111 to 2134
Spy0985	210-4768	sense	CTGAAGAGGGCCAAACACT	237	-63 to -43
	210-4771	antisense	TCGAAGAAGTAACCTTGATTAATGT	238	864 to 890
Spy1536	210-4772	sense	GCTCTAGTCGTTGAGAGCTAA	239	-90 to -66
	210-4775	antisense	TGTCTATCTGGTCAACCGTTT	240	1089 to 1112
Spy1666	210-4780	sense	GTGGCTAAGTCAGTCCTGCT	241	-80 to -59
	210-4783	antisense	AAGTTTTATTCGTTTGCAAGG	242	1055 to 1079
Spy1727	210-4776	sense	GATCATTGACTAAGTAGGCCAAACAA	243	-76 to -49
	210-4779	antisense	CCAAAAACGTCATGCCAAC	244	879 to 898

RESULTS

Gene conservation analysis of selected streptococcal antigens

- 5 The PCR and sequencing of the 9 selected genes was performed as described under Methods. Table 3 shows the strains used for sequencing, while Table 4 lists the oligonucleotides employed for the PCR and sequencing analyses.

Sequence analyses of Spy0269

- 10 Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 98.7% to 100% as compared to the sequence of Spy0269 from *S. pyogenes* SF370. Table 5 lists all 36 amino acid positions which showed a distinct amino acid as compared to Spy0269 from *S. pyogenes* SF370.
- 15 **Table 5: Gene conservation of Spy0269.**¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	AA change ²	Strains with the respective change ¹	Strains with the respective change ²
30	30	V	I		Schm1_142, Schm1_177, Schm1_43, RDN75	
68	68	D	E		Schm1_76, Schm1_92, Schm1_142, Schm1_176, Schm1_177, Schm1_25, Schm1_43, Schm2_32, RDN136, RDN75	
73	73	T	A		Schm1_142, Schm1_177, Schm1_43	

80	80	E	K		Schm1_55, Schm1_68, Schm1_3, Schm2_23, Schm2_30
83	83	E	K		Schm1_17, Schm1_59, Schm1_97
94	94	E	K		Schm1_142, Schm1_177, Schm1_43
97	97	H	N		Schm1_99, Schm2_14, Schm2_46
150	150	A	V		Schm1_74, Schm1_35, Schm1_141, Schm1_174, Schm1_41, Schm2_9, Schm2_50, RDN60, RDN78, RDN75
230	230	A	G		Schm1_35
249	249	E	D		Schm1_103
276	276	A	V		Schm1_56, Schm1_106
279	279	G	D		Schm1_55, Schm1_68, Schm1_3, Schm2_23, Schm2_30
307	307	A	G		Schm1_92
482	482	H	R		Schm1_17, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_108, Schm1_141, Schm1_174, Schm1_176, Schm1_177, Schm1_25, Schm1_43, Schm1_59, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN116
485	485	N	K		Schm1_39, Schm1_55, Schm1_68, Schm1_156, Schm1_248, Schm1_3,

					Schm1_22, Schm1_29, Schm2_23, Schm2_30, RDN75
537	537	G	S		Schm1_76, Schm1_92, Schm1_142, Schm1_176, Schm1_177, Schm1_25, Schm1_43, Schm2_32, RDN136
577	577	Q	E		Schm1_39, Schm1_76, Schm1_92, Schm1_142, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_29, Schm1_43, Schm2_32, Schm2_50, RDN60, RDN136
602	602	G	R		Schm2_46
605	605	R	K		Schm1_174
610	610	A	V		Schm1_74, Schm1_76, Schm1_35, Schm1_176, Schm1_25, Schm1_41, Schm2_9, Schm2_32, RDN136, RDN78
636	636	L	M		Schm1_74, Schm1_76, Schm1_35, Schm1_176, Schm1_25, Schm1_41, Schm2_9, Schm2_32, RDN136, RDN78
640	640	E	K		Schm1_74, Schm1_76, Schm1_35, Schm1_176, Schm1_25, Schm1_41, Schm2_9, Schm2_32, RDN136, RDN78
641	641	A	V		Schm1_56,

				Schm1_108	
650	650	V	E	Schm2_9	
666	666	F	L	Schm1_22	
700	700	A	T	Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_253, Schm1_68, Schm1_108, Schm1_156, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_59, Schm1_97, Schm1_123, Schm1_136, Schm2_23, Schm2_30, RDN02, RDN120, RDN116	
703	703	A	V	Schm2_50, RDN60	
710	710	S	G	Schm1_17, Schm1_59, Schm1_97	
733	733	E	G	Schm1_56, Schm1_108	
750	750	A	P	Schm1_22	
752	752	P	S	Schm1_55, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_68, Schm1_176, Schm1_177, Schm1_234, Schm1_3, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN136, RDN78	
758	758	P	L	Schm1_92	
764	764	I	V	Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194	

					Schm1_35, Schm1_176, Schm1_177, Schm1_234, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_32, Schm2_46, RDN136, RDN78	
765	765	D	E		Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_176, Schm1_177, Schm1_234, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_32, Schm2_46, RDN136, RDN78	
794	794	L	F	H	Schm1_22	Schm2_23, Schm2_30
873	873	K	R		Schm1_55, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_68, Schm1_141, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_3, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50,	

					RDN60, RDN136, RDN78, RDN75	
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Sequence analyses of Spy0292

Sequences were obtained from all 51 strains. The level of amino acid sequence identity

5 ranged from 97.3% to 100% as compared to the sequence of Spy0292 from *S. pyogenes* SF370. Table 6 lists all 36 amino acid positions which showed a distinct amino acid as compared to Spy0292 from *S. pyogenes* SF370.

10 **Table 6: Gene conservation of Spy0292.** ¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. ², second possible amino acid observed at the respective position. ³, third possible amino acid observed at the respective position.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	AA change ²	AA change ³	Strains with respective change ¹	Strains with respective change ²	Strains with respective change ³
21	21	S	N			Schm1_136		
32	32	A	V			RDN02		
45	45	E	K			RDN60		
48	48	A	T			Schm1_56, Schm1_108, Schm1_85		
50	50	E	K			RDN76		
57	57	V	I			Schm2_50		
58	58	S	T			Schm2_50		
65	65	L	M			Schm1_141, Schm1_156, Schm1_174		
68	68	K	Q	N		Schm2_30	Schm2_50	
88	88	Y	D			Schm2_30		
89	89	E	D			Schm2_30		
93	93	N	Y			Schm2_50		
95	95	T	S			Schm2_30		
96	96	I	M			Schm2_30		
101	101	L	P			Schm2_30		
121	121	N	I			Schm2_50		
122	122	S	T			Schm2_50		
128	128	A	P	S		RDN60	RDN60	
137	137	K	N			Schm2_30		
141	141	K	E	Q		Schm1_17	Schm2_50	
147	147	R	L	W	I	Schm1_17	Schm2_50	RDN60
148	148	Q	L			Schm2_30, RDN60		
152	152	S	F			RDN120		
154	154	A	T			Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30		
165	165	H	L			RDN60		

188	188	L	F		Schm1_174	
189	189	A	P		Schm1_174	
190	190	I	V		Schm1_253, Schm1_123	
214	214	A	D		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_25, Schm1_43, Schm1_59, Schm1_85, Schm1_99, Schm1_103, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120	
240	240	V	I		Schm1_92, RDN120	
266	266	L	I		Schm1_144, Schm1_234, Schm1_103	
309	309	Y	S		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97	

					Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116		
314	314	P	S		Schm1_17, Schm1_22, Schm1_97		
351	351	A	P		Schm1_177		
371	371	G	A		Schm1_234		
386	386	Q	H		Schm1_234		

Sequence analyses of Spy0416

Sequences were obtained from all 50 strains excluding strain Schmitz 1/74. The level of amino acid sequence identity ranged from 98.1% to 100% as compared to the sequence of Spy0416 from *S. pyogenes* SF370. Table 7 lists all 103 amino acid positions which showed a distinct amino acid as compared to Spy0416 from *S. pyogenes* SF370. The gene showed in addition an insertion of 2 amino acids after position 31, as well as several deletions of amino acids at the indicated positions (e.g. strains Schmitz 1/17 and Schmitz 1/39).

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Table 7: Gene conservation of Spy0416.¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains.², second possible amino acid observed at the respective position. Deletion or insertion refers to a missing or additional amino acid relative to Spy0416 of *S. pyogenes* SF370.

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Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	AA change ²	Strains with respective change ¹	Strains with respective change ²
21	21	I	V		Schm1_99, Schm2_46	
27	27	V	M		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156,	

					Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN78, RDN120, RDN75, RDN116
29	29	T	M		Schm1_17, Schm1_39, Schm1_76, Schm1_142, Schm1_35, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm1_97, Schm1_136, Schm2_9, Schm2_14, RDN136, RDN78, RDN5
Insertion	32	-	T		Schm1_17, Schm1_39, Schm1_76, Schm1_142, Schm1_35, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_41,

					Schm1_43, Schm1_59, Schm1_97, Schm1_136, Schm2_9, Schm2_14, RDN136, RDN78
Insertion	33	-	T		Schm1_17, Schm1_22, Schm1_97
38	40	S	T		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN136, RDN78, RDN116
40	42	M	T		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177,

					Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_138, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN136, RDN78, RDN116
49	51	A	T	.	Schm1_39, Schm1_76, Schm1_142, Schm1_35, Schm1_176, Schm1_177, Schm1_248, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm2_9, Schm2_14, Schm2_32, RDN60, RDN136, RDN78
54	56	Q	P	.	Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30
55	57	H	P	.	Schm1_55, Schm1_253, Schm1_68, Schm1_3, Schm1_29, Schm1_99, Schm1_123, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN116
67	69	K	Q	.	Schm1_17, Schm1_55, Schm1_56, Schm1_253, Schm1_68, Schm1_108,

					Schm1_3, Schm1_22, Schm1_29, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN120, RDN116
68	70	S	P	T	Schm1_39, Schm1_55, Schm1_76, Schm1_142, Schm1_35, Schm1_68, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm2_9, Schm2_14, Schm2_23, Schm2_30, RDN136, RDN78, RDN5
69	71	Q	P		Schm1_17, Schm1_56, Schm1_253, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_32, Schm2_46, Schm2_50, RDN120, RDN116
71	73	T	I		Schm1_253, Schm1_123, Schm2_32
74	76	I	V		Schm1_55, Schm1_253, Schm1_68, Schm1_3, Schm1_29, Schm1_99, Schm1_123, Schm1_136

					Schm2_23, Schm2_30, Schm2_46	
76	78	L	P		Schm1_17, Schm1_55, Schm1_56, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_234, Schm1_3, Schm1_22, Schm1_29, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_46, Schm2_50, RDN60, RDN02, RDN116	
77	79	K	E		Schm1_55, Schm1_253, Schm1_68, Schm1_3, Schm1_29, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_46	
78	80	T	I		Schm1_56, Schm1_108, Schm1_85, Schm2_50	
85	87	S	P		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41,	

					Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_50, RDN60, RDN136, RDN78
87	89	D	G		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_50, RDN60, RDN136, RDN78
91	93	E	K		Schm1_99, Schm2_46, RDN116
93	95	T	Deletion		RDN60
102	104	A	S		RDN120, RDN75, RDN116
104	106	S	P		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108,

					Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_99, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN78, RDN120, RDN75, RDN116
107	109	N	Deletion		Schm1_92
110	112	S	P		Schm1_17, Schm1_39, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_35, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN78, RDN120, RDN75, RDN116
183	185	A	V		RDN75

215	217	E	G		Schm1_17, Schm1_92, Schm1_22, Schm1_97, Schm1_99, Schm2_46, RDN116	
228	230	A	Deletion		Schm1_17, Schm1_56, Schm1_92, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm2_50, RDN120	
229	231	E	Deletion	D	Schm1_17, Schm1_56, Schm1_92, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm2_50, RDN120, RDN116	Schm1_144, Schm1_194, Schm1_253, Schm1_234, Schm1_99, Schm1_123, Schm1_136, Schm2_46, RDN02
230	232	A	Deletion		RDN116	
238	240	H	N		Schm1_17, Schm1_92, Schm1_22, Schm1_97	
273	275	D	E		Schm1_92, Schm1_99, Schm2_46, RDN120, RDN116	
308	310	A	T		Schm1_56, Schm1_108, Schm1_85, Schm2_50	
320	322	I	V		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41,	

					Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
428	430	T	A		Schm1_142
429	431	V	A		Schm1_17, Schm1_22, Schm1_97
431	433	E	G		Schm1_253, Schm1_123
434	436	N	S		RDN116
449	451	V	F		Schm1_177
453	455	D	N		Schm1_142, Schm1_35, Schm1_141, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm1_97, Schm1_123, Schm1_136, Schm2_9, RDN136
463	465	S	T		Schm1_177, RDN136
478	480	N	K		Schm1_17, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_176, Schm1_177, Schm1_234, Schm1_22, Schm1_25, Schm1_43, Schm1_97, RDN60, RDN02, RDN136, RDN120, RDN116

481	483	D	N	Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm1_136, Schm2_23, Schm2_30	
484	486	G	D	Schm1_17, Schm1_92, Schm1_144, Schm1_194, Schm1_234, Schm1_22, Schm1_97, RDN02	
493	495	P	L	RDN120	
512	514	V	L	Schm1_253, Schm1_123	
519	521	P	S	Schm1_253, Schm1_123	
530	532	A	S	Schm1_141, Schm1_156, Schm1_174	
535	537	I	V	RDN120	
547	549	A	V	Schm1_35, Schm1_41, Schm2_9	
553	555	G	T	RDN116	
560	562	E	V	RDN02, RDN116	
630	632	V	I	RDN75	
668	670	T	M	RDN116	
689	691	G	D	Schm1_39, Schm1_248, Schm1_59, Schm2_14	
706	708	I	V	RDN02	
723	725	D	A	Schm1_39, Schm1_55, Schm1_56, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_234, Schm1_248, Schm1_3, Schm1_29, Schm1_41, Schm1_59, Schm1_85, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_50, RDN60,	

					RDN02, RDN78, RDN120, RDN116
734	736	T	A		RDN02
743	745	R	H		RDN116
749	751	H	R		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN60, RDN02, RDN136, RDN78, RDN120, RON75, RDN116
770	772	R	K		RDN60, RDN120
804	806	D	A		Schm1_55, Schm1_68, Schm1_248, Schm1_3, Schm1_29, Schm2_23, Schm2_30, RDN02, RDN120, RDN75
874	876	T	M		Schm1_35,

					Schm1_41, Schm1_103, Schm1_136, Schm2_9, RDN78
876	878	S	C		Schm1_94
913	915	N	S		RDN60
951	953	P	S		Schm1_76, Schm1_177, Schm1_43
991	993	H	Y		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_46, Schm2_50, RDN60, RDN02, RDN78, RDN120, RDN116
1053	1055	V	A		Schm1_94, Schm1_12X, Schm1_5
1078	1080	E	A		Schm1_92, Schm1_142, Schm1_176, Schm1_25, Schm1_99, Schm2_23, Schm2_30, Schm2_46
1080	1082	N	S		Schm1_35, Schm1_41, Schm2_9, RDN78
1227	1229	T	I		Schm1_76
1238	1240	V	A		Schm1_17, Schm1_39,

					Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RON120, RON75, RON116
1241	1243	I	V		Schm1_253, Schm1_123
1302	1304	D	G		Schm1_253, Schm1_123
1313	1315	D	G		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_94, Schm1_142, Schm1_144, Schm1_253, Schm1_12X, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156,

				Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_5, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
1322	1324	V	I	RDN120
1349	1351	V	M	RDN02
1355	1357	P	S	Schm1_234, Schm1_136, RDN75
1364	1366	R	E	Schm1_156
1365	1367	D	I	Schm1_156
1393	1395	A	V	Schm1_35, Schm1_41, Schm2_9, RDN78
1425	1427	A	V	RDN02
1479	1481	N	K	RDN60
1483	1485	V	I	Schm1_141, Schm1_156, Schm1_174
1487	1489	I	M	Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_58, Schm1_108, Schm1_141, Schm1_156, Schm1_174,

				Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
1505	1507	E	K	Schm2_50
1516	1518	D	G	Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136

				Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
1522	1524	E	G	Schm1_99, Schm2_32, Schm2_46
1538	1540	G	D	Schm1_17, Schm1_22, Schm1_97
1545	1547	S	T	Schm2_50
1555	1557	N	D	Schm1_35, Schm1_41, Schm2_9, RDN78
1560	1562	T	A	Schm1_17, Schm1_144, Schm1_194, Schm1_35, Schm1_234, Schm1_22, Schm1_41, Schm1_97, Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_32, Schm2_46, RDN78
1576	1578	G	R	Schm2_50
1580	1582	D	G	Schm1_144, Schm1_194, Schm1_234, Schm1_136
1587	1589	V	A	Schm1_142, Schm1_176, Schm1_25
1591	1593	N	S	RDN75
1598	1600	A	V	Schm1_17, Schm1_22, Schm1_97
1605	1607	S	T	Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108,

					Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
1608	1610	S	P		Schm1_144, Schm1_194, Schm1_234, Schm1_136	
1609	1611	A	Deletion		Schm1_142, Schm1_176, Schm1_25, RDN120	
1610	1612	T	Deletion		Schm1_142, Schm1_176, Schm1_25, RDN120	
1617	1619	T	A		Schm1_17, Schm1_39, Schm1_56, Schm1_92, Schm1_35, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_248, Schm1_22, Schm1_41, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm2_9, Schm2_14, Schm2_23	

					Schm2_30, Schm2_46, Schm2_50, RDN60, RDN78, RDN116	
1622	1624	G	S		Schm1_142, Schm1_178, Schm1_25, RDN120	
1642	1644	K	T		Schm1_144	

Sequence analyses of Spy0488

Sequences were obtained from all 51 strains. The level of amino acid sequence identity
5 ranged from 85.4% to 100% as compared to the sequence of Spy0488 from *S. pyogenes* SF370. Table 8 lists all 49 amino acid positions which showed a distinct amino acid as compared to Spy0488 from *S. pyogenes* SF370. The genes from several strains (e.g. Schmitz 1/55) possessed furthermore a different N terminus, with an addition of 25 amino acids and a frame-shift for the first 16 amino acids relative to Spy0488 from *S. pyogenes* SF370.
10

Table 8: Gene conservation of Spy0488.¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. ², second possible amino acid observed at the respective position. Insertion refers to an additional amino acid relative to Spy0488 of *S. pyogenes* SF370.
15

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	AA change ²	Strains with respective change ¹	Strains with respective change ²
Insertion	1	-	M		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85,	

				Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	2	-	M	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	3	-	M	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177,

				Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	4	-	L	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	5	-	R	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	6	-	D	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174,

				Schm1_175, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	7	-	V	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	8	-	K	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	9	-	V	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141,

					Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	10	-	K		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	11	-	M	T	Schm1_39, Schm1_55, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN60, RDN136, RDN78, RDN120, RDN75	Schm1_56, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm2_50, RDN02, RDN116
Insertion	12	-	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177,	

				Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	13	-	S	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	14	-	L	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	15	-	L	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174,	

				Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN16
Insertion	16	-	V	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN16
Insertion	17	-	G	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN16
Insertion	18	-	C	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141,

				Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	19	-	A	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	20	-	A	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	21	-	T	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68,

				Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	22	-	L	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	23	-	L	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
Insertion	24	-	V	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253,

					Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	25	-	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
2	27	R	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
3	28	Q	S	G	Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_68, Schm1_106,	Schm1_74, Schm1_92, Schm1_144, Schm1_194,

					Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN75, RDN116	Schm1_35, Schm1_234, Schm1_41, Schm1_103, Schm2_9, RDN78
4	29	I	T		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
5	30	Q	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
6	31	S	A		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174,	

				Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN16
7	32	I	A	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN16
8	33	R	D	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN16
9	34	L	S	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141,

					Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
10	35	I	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
11	36	D	H		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
12	37	V	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68,

				Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
13	38	L	S	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN75, RDN116	RDN78
14	39	E	D	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
15	40	L	R	Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253,	

					Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
16	41	A	R		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_58, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
30	55	S	F		Schm1_99, Schm1_136, Schm2_46
35	60	S	Y		RDN75
50	75	A	T		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
53	78	N	D		Schm1_253, Schm1_99, Schm1_123, Schm1_136,

					Schm2_46, RDN120
56	81	S	Y		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_144, Schm1_194, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN75, RDN116
60	85	D	G		Schm1_248, Schm1_59
69	94	D	G		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_253, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120
75	100	Q	H		Schm2_32
76	101	I	T		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_144, Schm1_194, Schm1_253, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120
87	112	F	L		Schm1_253, Schm1_123
93	118	G	E		Schm1_99, Schm2_46
112	137	V	A		Schm1_253, Schm1_123
117	142	I	T		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_29,

				Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
127	152	H	Y	Schm1_39
157	182	D	G	RDN75
163	188	V	L	RDN75
174	199	K	T	Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30
183	208	G	R	RDN75
184	209	G	S	Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02
188	213	F	L	Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_234, Schm1_41, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_46, RDN78
198	223	P	S	Schm1_92
199	224	K	R	Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02
201	226	R	G	Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_108, Schm1_177, Schm1_234, Schm1_41, Schm1_43, Schm1_85, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_32, Schm2_46, Schm2_50, RDN02, RDN136, RDN78, RDN120
202	227	Q	L	Schm1_144, Schm1_194, Schm1_35, Schm1_234, Schm1_41, Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_46, RDN78
206	231	T	I	Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02
209	234	D	A	Schm1_92, Schm1_144, Schm1_194, Schm1_35, Schm1_234, Schm1_41, Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_46, RDN78
217	242	P	S	Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02
221	246	W	C	Schm1_76, Schm1_177, Schm1_43, RDN136
222	247	K	E	Schm1_56, Schm1_108,

					Schm1_85, Schm2_50, RDN02
232	257	A	T		Schm1_39, Schm1_22, Schm1_97
235	260	S	F		Schm1_253, Schm1_123
238	263	T	I		Schm1_248, Schm1_59
258	283	A	V		Schm1_92
291	316	E	Q		Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30

Sequence analyses of Spy0872

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 98.2% to 100% as compared to the sequence of Spy0872 from *S. pyogenes* SF370. Table 9 lists all 34 acid positions which showed a distinct amino acid as compared to Spy0872 from *S. pyogenes* SF370. The gene from strain Schmitz 1/22 showed in addition an insertion of 2 amino acids after position 587.

Table 9: Gene conservation of Spy0872.¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. Insertion refers to an additional amino acid relative to Spy0872 of *S. pyogenes* SF370.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	Strains with respective change ¹
67	67	G	C	Schm1_136
74	74	E	D	Schm1_76, Schm1_177, Schm1_43, RDN136
178	178	K	N	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
181	181	P	S	RDN60
222	222	H	Y	RDN120
228	228	V	A	Schm1_56, Schm1_108, Schm1_85, Schm2_50
253	253	V	I	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_144, Schm1_194, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN120
328	328	I	M	Schm1_55, Schm1_56, Schm1_92, Schm1_68, Schm1_108, Schm1_3, Schm1_29, Schm1_85, Schm1_136, Schm2_23, Schm2_30, Schm2_50, RDN75

329	329	K	T	Schm1_55, Schm1_56, Schm1_92, Schm1_68, Schm1_108, Schm1_3, Schm1_29, Schm1_85, Schm1_136, Schm2_23, Schm2_30, Schm2_50, RDN75
336	336	V	I	Schm1_56, Schm1_108, Schm1_85, Schm2_50
337	337	A	T	Schm1_136, RDN75
340	340	P	L	RDN120
393	393	A	V	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
412	412	M	I	RDN120
427	427	D	Y	Schm2_46
433	433	G	E	Schm1_7, Schm1_22, Schm1_97
444	444	I	T	RDN75
478	478	Y	F	Schm1_253, Schm1_123
490	490	T	I	Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30
492	492	F	C	RDN02
532	532	A	T	Schm1_144, Schm1_194, Schm1_234, Schm1_103
535	535	I	V	Schm1_142, Schm1_176, Schm1_25, Schm2_46, RDN116
553	553	E	Q	Schm1_142, Schm1_176, Schm1_25, Schm1_99, Schm2_32, Schm2_46, RDN116
576	576	S	R	Schm1_142, Schm1_176, Schm1_25, Schm1_99, Schm2_46, RDN116
580	580	V	-	I
Insertion	588	-	I	Schm1_7, Schm1_22, Schm1_97
Insertion	589	-	I	Schm1_7, Schm1_22, Schm1_97
588	590	I	T	RDN78
598	600	G	D	Schm1_92
600	602	T	I	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
605	607	V	I	Schm1_7, Schm1_39, Schm1_56, Schm1_76, Schm1_144, Schm1_194, Schm1_253, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_22, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm2_14, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120
620	622	L	F	Schm1_7, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm1_99, Schm2_32, Schm2_46, RDN116
625	627	T	I	Schm1_7, Schm1_22, Schm1_97
634	636	S	N	Schm1_7, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm1_99, Schm2_46, RDN116

659	661	G	C	Schm1_253, Schm1_123
667	669	K	E	Schm1_144, Schm1_194, Schm1_234, Schm1_103, RDN120

Sequence analyses of Spy0895

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 98.9% to 100% as compared to the sequence of Spy0895 from *S. pyogenes* SF370. Table 10 lists all 13 amino acid positions which showed a distinct amino acid as compared to Spy0895 from *S. pyogenes* SF370.

Table 10: Gene conservation of Spy0895.¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	Strains with respective change ¹
19	19	A	V	Schm1_17, Schm1_22, Schm1_97
33	33	A	V	Schm1_17, Schm1_141, Schm1_156, Schm1_174, Schm1_22, Schm1_97, RDN02
50	50	F	V	Schm1_253, Schm1_123
52	52	A	V	Schm1_17, Schm1_55, Schm1_68, Schm1_141, Schm1_156, Schm1_174, Schm1_3, Schm1_22, Schm1_29, Schm1_97, Schm2_30
60	60	T	I	Schm1_56, Schm1_108, Schm1_85, Schm2_50
71	71	L	I	Schm1_92, Schm1_144, Schm1_194, Schm1_234, Schm1_103
138	138	H	Q	Schm1_92, Schm1_144, Schm1_194, Schm1_234, Schm1_103
188	188	R	P	Schm1_174
238	238	R	C	Schm1_55, Schm1_76, Schm1_68, Schm1_177, Schm1_3, Schm1_29, Schm1_43, Schm2_30, RDN136
242	242	Y	C	Schm1_136
252	252	K	T	Schm1_56, Schm1_108, Schm1_85, Schm2_50
255	255	S	G	Schm1_56, Schm1_108, Schm1_85, Schm2_50
256	256	L	F	RDN60

Sequence analyses of Spy1536

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 99.1% to 100% as compared to the sequence of Spy1536 from *S. pyogenes* SF370. Table 11 lists all 8 amino acid positions which showed a distinct amino acid as compared to Spy1536 from *S. pyogenes* SF370. The gene from strain Schmitz 2/14 showed in addition an insertion of 3 amino acids after position 207.

Table 11: Gene conservation of Spy1536.¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. Insertion refers to an additional amino acid relative to Spy1536 of *S. pyogenes* SF370.

5

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	Strains with respective change ¹
5	5	K	N	Schm1_12, Schm2_9, Schm1_136
92	92	G	R	Schm1_142
97	97	A	T	Schm1_5, Schm1_74
125	125	P	S	Schm1_123
126	126	V	A	Schm1_142
183	183	V	I	Schm1_94, RDN78, Schm1_97, Schm1_59, Schm1_76, RDN136, Schm1_177, Schm2_32, Schm1_141, Schm1_144, RDN120, Schm1_25, Schm1_176, RDN75_85, Schm2_46, Schm2_23, Schm1_55
Insertion	208	-	K	Schm2_14
Insertion	209	-	N	Schm2_14
Insertion	210	-	G	Schm2_14
333	336	V	I	Schm1_12, Schm1_35, Schm2_9, Schm1_174, Schm1_136, Schm1_234, Schm1_68
337	340	Q	E	Schm1_43, Schm1_108

Sequence analyses of Spy1666

Sequences were obtained from 50 strains. The sequence from strain RDN120 was not determined. The level of amino acid sequence identity ranged from 98.2 to 100% as compared to the sequence of Spy1666 from *S. pyogenes* SF370. Table 12 lists all 18 amino acid positions which showed a distinct amino acid as compared to Spy1666 from *S. pyogenes* SF370.

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Table 12: Gene conservation of Spy1666.¹, observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change ¹	Strains with respective change ¹
3	3	S	P	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
11	11	L	V	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
45	45	D	N	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
67	67	G	S	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
69	69	E	Q	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
90	90	K	Q	Schm1_142, Schm1_176, Schm1_25, Schm2_46, Schm1_142, Schm1_176, Schm1_25, Schm2_46
106	106	R	I	RDN136, RDN78, RDN136, RDN78

120	120	I	F	Schm1_136, Schm1_136 RDN78, RDN78
149	149	L	S	RDN75, RDN75
167	167	T	N	
204	204	T	A	Schm1_253, Schm1_103, Schm1_123, Schm1_253, Schm1_103, Schm1_123
217	217	P	S	Schm1_39, Schm1_248, Schm1_59, Schm1_39, Schm1_248, Schm1_59
251	251	Q	H	Schm1_97, Schm1_97
252	252	D	E	Schm1_76, Schm1_141, Schm1_155, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136, Schm1_76, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136
259	259	L	F	Schm1_92, RDN75, Schm1_92, RDN75 RDN116, RDN116
292	292	L	F	
302	302	K	T	Schm1_17, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm2_46, Schm1_17, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm2_46
319	319	T	A	Schm1_76, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136, Schm1_76, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136

Sequence analyses of Spy1727

No sequence variation was observed on the amino acid sequence level in any of the
5 analyzed 51 gene sequences obtained from the listed *S. pyogenes* strains.

SEQUENCE DATA FOR AMINO ACID SEQUENCES

1. Spy0269

1.1 Full length Spy0269

> Spy0269 / SF370 (serotype 1); SEQ ID NO: 57
MDLEQTQPKVQKIALTSTIALLSASVGVSHQVKADDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKT
LSQQKAELTELATLTTAEINHLKEQQDNEQKALTSQAQEITYTNTLASSEETLLAAGQAEHQRELTATETELH
NAQADQHSKETALSESEQKASISETAERQLDVEQVKTSEQNIAKLNAMISNPDAITKAAQATNDNTKALSS
10 KAKADLENQAKAVKKQLEELAALAAKEAEISRLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIG
SASYNYYKEHADQIIAKASPGNQLNQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEV
QNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPE
15 QNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPE
VQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPE
VQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPE
EKEYRNLDEDIATVPDLQVAPPPLTVQPKLPSYSKIDTPTLVQEMVKEITQQLLEASARLAANENTSLVAE
20 LVGQT
SEMVASNAIVSKITSSITQPSSKTSYSGSSTSNSLISDVDESTQRALKAGVVLMAAVGLTGFRFRKESK

20 1.2 Antigenic fragment Spy0269-1

> Spy0269-1 / SF370 (serotype 1); SEQ ID NO: 1
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATLTTAEINHLKEQQDNEQKAL
TSAQEITYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSESEQKASISETAERQLDVEQVKT
25 SEQNIAKLNAMISNPDAITKAAQATNDNTKALSSLEAKADLENQAKAVKKQLEELAALAAKEAEIS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEHADQIIAKASPGNQLNQYQDIPAD
DRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPAD
20 DRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPAD
VSGHYGVPHDKTIIEDSAGASGLIRNDNMENYGAFNDVHTVNGIKRGYDYSIKYMLFTDHLHGNTYGHAI
NFLRVDKHNPNAV

30 1.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0269-1 / Schmitz 2/14 (serotype 1); SEQ ID NO: 58
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATLTTAEINHLKEQQDNEQKAL
35 TSAQEITYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSESEQKASISETAERQLDVEQVKT
SEQNIAKLNAMISNPDAITKAAQATNDNTKALSSLEAKADLENQAKAVKKQLEELAALAAKEAEIS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEHADQIIAKASPGNQLNQYQDIPAD
DRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPAD
40 DRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPAD
VFLRVDKRNPNAV

> Spy0269-1 / Schmitz 1/156 (serotype 4); SEQ ID NO: 59
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATLTTAEINHLKEQQDNEQKAL
TSAQEITYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSESEQKASISETAERQLDVEQVKT
45 SEQNIAKLNAMISNPDAITKAAQATNDNTKALSSLEAKADLENQAKAVKKQLEELAALAAKEAEIS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEHADQIIAKASPGNQLNQYQDIPAD
DRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPAD
50 DRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPAD
VSGHYGVPHDKTIIEDSAGASGLIRNDNMENYGAFNDVHTVNGIKRGYDYSIKYMLFTDHLHGNTYGHAI
NFLRVDKHNPKAV

50 > Spy0269-1 / Schmitz 1/59 (serotype 12); SEQ ID NO: 60

DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATLTTAEINHLKEQQDNEQKAL
TSAQEITYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSESEQKASISETAERQLDVEQVKT
55 SEQNIAKLNAMISNPDAITKAAQATNDNTKALSSLEAKADLENQAKAVKKQLEELAALAAKEAEIS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEHADQIIAKASPGNQLNQYQDIPAD
DRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPADRNRFDPDNLTPEVQNLQYQDIPAD
VSGHYGVPHDKTIIEDSAGASGLIRNDNMENYGAFNDVHTVNGIKRGYDYSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAV

- > Spy0269-1 / Schmitz 1/177 (serotype 22); SEQ ID NO: 61
 DDRASGETKASNTHDDSLPKPETIQEAKATIEAVEKALSQQKAELTELATALTAKTTAKINHLKEQQDNEQKAL
 TSAQEITYNTLASSETTLAOGAEHQRELTATETELHNQAQDQHSKETALSEQKASIAETTRAQDLVEQVKT
 SEONIAKLNAMISNPDAITKAQAQTANDNTKALSELEKAKADLENQAKAVKKQLTEELAAQKAALAEKEAELS
 5 RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEADQIIAKASPGNQLNQYQDIPA
 DRNRFVDPDNLTPEVQNELAQFAAHMINSVRQLGLPPVTAGSQEFARLLSTSJKTHGNTRSPSFVYQPG
 VSGHYGVGPBHDKTIIEDSAGASGLIRNDNNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
 NFLRVDKRNPNAV
- 10 > Spy0269-1 / Schmitz 1/43 (serotype 22); SEQ ID NO: 62
 DDRASGETKASNTHDDSLPKPETIQEAKATIEAVEKALSQQKAELTELATALTAKTTAKINHLKEQQDNEQKAL
 TSAQEITYNTLASSETTLAOGAEHQRELTATETELHNQAQDQHSKETALSEQKASIAETTRAQDLVEQVKT
 SEONIAKLNAMISNPDAITKAQAQTANDNTKALSELEKAKADLENQAKAVKKQLTEELAAQKAALAEKEAELS
 15 RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEADQIIAKASPGNQLNQYQDIPA
 DRNRFVDPDNLTPEVQNELAQFAAHMINSVRQLGLPPVTAGSQEFARLLSTSJKTHGNTRSPSFVYQPG
 VSGHYGVGPBHDKTIIEDSAGASGLIRNDNNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
 NFLRVDKRNPNAV
- > Spy0269-1 / Schmitz 1/136 (serotype 25); SEQ ID NO: 63
 20 DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQSKAELTELATALTAKTTAEINHLKEQQDNEQKAL
 TSAQEITYNTLASSETTLAOGAEHQRELTATETELHNQAQDQHSKETALSEQKASIAETTRAQDLVEQVKT
 SEONIAKLNAMISNPDAITKAQAQTANDNTKALSELEKAKADLENQAKAVKKQLTEELAAQKAALAEKEAELS
 RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEADQIIAKASPGNQLNQYQDIPA
 25 DRNRFVDPDNLTPEVQNELAQFAAHMINSVRQLGLPPVTAGSQEFARLLSTSJKTHGNTRSPSFVYQPG
 VSGHYGVGPBHDKTIIEDSAGASGLIRNDNNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
 NFLRVDKRNPNAV
- > Spy0269-1 / Schmitz 1/85 (serotype 28); SEQ ID NO: 64
 30 DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQSKAELTELATALTAKTTAEINHLKEQQDNEQKAL
 TSAQEITYNTLASSETTLAOGAEHQRELTATETELHNQAQDQHSKETALSEQKASIAETTRAQDLVEQVKT
 SEONIAKLNAMISNPDAITKAQAQTANDNTKALSELEKAKADLENQAKAVKKQLTEELAAQKAALAEKEAELS
 RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEADQIIAKASPGNQLNQYQDIPA
 35 DRNRFVDPDNLTPEVQNELAQFAAHMINSVRQLGLPPVTAGSQEFARLLSTSJKTHGNTRSPSFVYQPG
 VSGHYGVGPBHDKTIIEDSAGASGLIRNDNNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
 NFLRVDKRNPNAV
- > Spy0269-1 / Schmitz 2/50 (serotype 28); SEQ ID NO: 65
 40 DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQSKAELTELATALTAKTTAEINHLKEQQDNEQKAL
 TSAQEITYNTLASSETTLAOGAEHQRELTATETELHNQAQDQHSKETALSEQKASIAETTRAQDLVEQVKT
 SEONIAKLNAMISNPDAITKAQAQTANDNTKALSELEKAKADLENQAKAVKKQLTEELAAQKAALAEKEAELS
 RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEADQIIAKASPGNQLNQYQDIPA
 45 DRNRFVDPDNLTPEVQNELAQFAAHMINSVRQLGLPPVTAGSQEFARLLSTSJKTHGNTRSPSFVYQPG
 VSGHYGVGPBHDKTIIEDSAGASGLIRNDNNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
 NFLRVDKRNPNAV
- > Spy0269-1 / Schmitz 1/123 (serotype 49); SEQ ID NO: 66
 50 DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQSKAELTELATALTAKTTAEINHLKEQQDNEQKAL
 TSAQEITYNTLASSETTLAOGAEHQRELTATETELHNQAQDQHSKETALSEQKASIAETTRAQDLVEQVKT
 SEONIAKLNAMISNPDAITKAQAQTANDNTKALSELEKAKADLENQAKAVKKQLTEELAAQKAALAEKEAELS
 RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEADQIIAKASPGNQLNQYQDIPA
 55 DRNRFVDPDNLTPEVQNELAQFAAHMINSVRQLGLPPVTAGSQEFARLLSTSJKTHGNTRSPSFVYQPG
 VSGHYGVGPBHDKTIIEDSAGASGLIRNDNNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
 NFLRVDKRNPNAV
- > Spy0269-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 67
 60 DDRASGETKASNTHDDSLPKPETIQEAKATIEAVEKTLSQSKAELTELATALTAKTTAEINHLKEQQDNEQKAL
 TSAQEITYNTLASSETTLAOGAEHQRELTATETELHNQAQDQHSKETALSEQKASIAETTRAQDLVEQVKT
 SEONIAKLNAMISNPDAITKAQAQTANDNTKALSELEKAKADLENQAKAVKKQLTEELAAQKAALAEKEAELS
 RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNYYKEADQIIAKASPGNQLNQYQDIPA
 DRNRFVDPDNLTPEVQNELAQFAAHMINSVRQLGLPPVTAGSQEFARLLSTSJKTHGNTRSPSFVYQPG

VSGHYGVGPHDKTIIIEDSAGASGLIRNDDNMENIGAFNDVHTVNGIKRGYDYSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAVP

2. Spy0292

2.1 Full length Spy0292

> Spy0292 / SF370 (serotype 1); SEQ ID NO: 68
 MIKRLISLVLVIAFFAASTVSGEEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 10 KLNWDSPTVTSNYPYELTTNYTISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 RQWGISDAKVNSTGLTNHFLGANTYPNTEPDDENCFCATDLAIARHLLIEFPEVULKLSKSSTIFAGOTIY
 SYNYMLKGMPYCREGVDSLGFVGYSKKAGASFVATSVENQMVRITVVVLNADQSHEDDLAIFTTNTNOLLOYLLIN
 FOKVQLIENNKPVKTLVLDSPKTVKLVAQNSLFFIKPIHTKTKNTVHITKKSTMIAPLSKGQVLGRATLQ
 15 DKHLIGQGYLDTPPSINLILQKNISKSFFLKVVWNRFVRYVNDSL

2.2 Antigenic fragment Spy0292-1

> Spy0292-1 / SF370 (serotype 1); SEQ ID NO: 2
 EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 20 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

2.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0292-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 69
 EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 25 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 70
 EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 30 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDTKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 71
 EEYSVTAKHAIAVDLESGKVLYEKDTEKVEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 35 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/74 (serotype 3); SEQ ID NO: 72
 EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 40 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/76 (serotype 22); SEQ ID NO: 73
 EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 45 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/92 (serotype 11); SEQ ID NO: 74
 EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 50 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 75
 EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
 55 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGISDAKVNSTGLTNHFLG
 ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/142 (serotype 83); SEQ ID NO: 76

EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
ANTYPNTEPDDENCFC

5 > Spy0292-1 / Schmitz 1/144 (serotype 76); SEQ ID NO: 77
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
ANTYPNTEPDDENCFC

10 > Spy0292-1 / Schmitz 1/194 (serotype 44); SEQ ID NO: 78
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
ANTYPNTEPDDENCFC

15 2.4 Antigenic fragment Spy0292-3

> Spy0292-3 / SF370 (serotype 1); SEQ ID NO: 3
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
20 ANTPNTEPDDENCFCATDLAIARHLLLEFPEVVLKLSSKSSTIFDGTIYSYMLKGMPYCREGVDGLFVG
YSKKAGASFATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

25 2.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

25 > Spy0292-3 / Schmitz 1/39 (serotype 12); SEQ ID NO: 79
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIARHLLLEFPEVVLKLSSKSSTIFDGTIYSYMLKGMPYCREGVDGLFVG
YSKKAGASFATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

30 > Spy0292-3 / Schmitz 1/55 (serotype 118); SEQ ID NO: 80
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIARHLLLEFPEVVLKLSSKSSTIFDGTIYSYMLKGMPYCREGVDGLFVG
35 YSKKAGASFATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/56 (serotype 28); SEQ ID NO: 81
EEYSVTAKHIAAVDLESGKVLYEKDTKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
40 ANTPNTEPDDENCFCATDLAIARHLLLEFPEVVLKLSSKSSTIFDGTIYSYMLKGMPYCREGVDGLFVG
YSKKAGASFATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/74 (serotype 3); SEQ ID NO: 82
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
45 ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIARHLLLEFPEVVLKLSSKSSTIFDGTIYSYMLKGMPYCREGVDGLFVG
YSKKAGASFATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/76 (serotype 22); SEQ ID NO: 83
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
50 ANTPNTEPDDENCFCATDLAIARHLLLEFPEVVLKLSSKSSTIFDGTIYSYMLKGMPYCREGVDGLFVG
YSKKAGASFATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

55 > Spy0292-3 / Schmitz 1/92 (serotype 11); SEQ ID NO: 84
EEYSVTAKHIAAVDLESGKVLYEKDAKEVVPPAVASKLLTTVLVYKEVSKGKLNWDSPTVISNPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDMKKQLRQWGDISAKVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIARHLLLEFPEVVLKLSSKSSTIFDGTIYSYMLKGMPYCREGVDGLFIG
YSKKAGASFATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

- > Spy0292-3 / Schmitz 1/94 (serotype 1); SEQ ID NO: 85
 EEEYSVTAHKIAAVDLESQKVLYEKDAKEVVPPVASVSKLLTTVLVYKEVSKGKLNWDSPTVTISNYPYELETTNYT
 ISNVPLDKRKYTVEKELLSALVVNNANSPALAEAKIGGTPEKFVVDKMKQLRQWGISDAKVVNSTGLTNHFLG
 ANTYNPNTEPDDENCFCATDLAIARHLLLEFPFEVVLKLSSKSSTIFAGQTIIYSYNYMLKGMPCYREGVDGLFVG
 5 YSKKAGASFATSVENQMRVITVVNLADQSHEDDLAIFKTTNQLQYLLINFPQKVQLIE
- > Spy0292-3 / Schmitz 1/142 (serotype 83); SEQ ID NO: 86
 EEEYSVTAHKIAAVDLESQKVLYEKDAKEVVPPVASVSKLLTTVLVYKEVSKGKLNWDSPTVTISNYPYELETTNYT
 ISNVPLDKRKYTVEKELLSALVVNNANSPALAEAKIGGTPEKFVVDKMKQLRQWGISDAKVVNSTGLTNHFLG
 10 ANTYNPNTEPDDENCFCATDLAIARHLLLEFPFEVVLKLSSKSSTIFAGQTIIYSYNYMLKGMPCYREGVDGLFVG
 YSKKAGASFATSVENQMRVITVVNLADQSHEDDLAIFKTTNQLQYLLINFPQKVQLIE
- > Spy0292-3 / Schmitz 1/142 (serotype 76); SEQ ID NO: 87
 EEEYSVTAHKIAAVDLESQKVLYEKDAKEVVPPVASVSKLLTTVLVYKEVSKGKLNWDSPTVTISNYPYELETTNYT
 ISNVPLDKRKYTVEKELLSALVVNNANSPALAEAKIGGTPEKFVVDKMKQLRQWGISDAKVVNSTGLTNHFLG
 ANTYNPNTEPDDENCFCATDLAIARHLLLEFPFEVVLKLSSKSSTIFAGQTIIYSYNYMLKGMPCYREGVDGLFVG
 15 YSKKAGASFATSVENQMRVITVVNLADQSHEDDLAIFKTTNQLQYLLINFPQKVQLIE
- > Spy0292-3 / Schmitz 1/194 (serotype 44); SEQ ID NO: 88
 EEEYSVTAHKIAAVDLESQKVLYEKDAKEVVPPVASVSKLLTTVLVYKEVSKGKLNWDSPTVTISNYPYELETTNYT
 ISNVPLDKRKYTVEKELLSALVVNNANSPALAEAKIGGTPEKFVVDKMKQLRQWGISDAKVVNSTGLTNHFLG
 ANTYNPNTEPDDENCFCATDLAIARHLLLEFPFEVVLKLSSKSSTIFAGQTIIYSYNYMLKGMPCYREGVDGLFVG
 20 YSKKAGASFATSVENQMRVITVVNLADQSHEDDLAIFKTTNQLQYLLINFPQKVQLIE
- 25 3. Spy0416A
- 3.1 Full length Spy0416A
- > Spy0416A / SF370 (serotype 1); SEQ ID NO: 89
 30 ADELSTMSEPTITNHAQQQAQHLTNTELLSAESKSQDTSQITLKTNREKEQSQDLVSEPTTELADTDAAASMA
 NTGSQDATOKSASLPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGIDPAHOSMRISDVSTAKVSKEDMLA
 RQKAAGINYGSWINDKVFVAFNHYVENSNDNIKENQFEDFDEOWENFEDAEAPKAIKHHKKIYRPOSTQAPKET
 VIKTEETDGSHDIDWTQTTDDDTKYESHGMHVGTGIVAGNSKEAAATGERFLGIAPAEAQMFMRFVFANDIMGSAE
 SLFIKAIEDAVALGADVINSLSLTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSHDHDPPLATNPD
 35 YGLVGSPSTGRTPTSVAAINSKWIQLRMLTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
 STDAGYNAQDVKGKIALERDPNKTYDEMIALAKKHGALGVLFNNKPGQSNRSMRLTANGMGIPLSAFISHF
 GKMASQNLNGNTGTSLEFDVSVSKAPSQKGNEHMHSFNWLGSQDGLKPDITAPGGDIYSTYNDNHGSQTGTS
 MASPFQIAGASLLVKQYLEKTPQNLPKEKIADIVKNLLMSNAQIHVNPEKTTTSPRQQGAGLLNIDGAVTSGL
 40 YVTGKDNQYGSLSLGNIDTMTDFVTVHNLSNLDKTRYDTELLTDHVDPQKGRFTLTSHSLKTYQGGEVTVP
 NGKTVTRVMTDVSQFTKELTQMGPNGYLEGFVRFRDSQDQLNRVNIPFVGFKGQFENLAVAEEESIYRLKSQ
 GKTGFYFDESGPKDDIYVGKHTCLVTLGSE
- 3.2 Antigenic fragment Spy0416A-1
- > Spy0416A-1 / SF370 (serotype 1); SEQ ID NO: 4
 45 ADELSTMSEPTITNHAQQQAQHLTNTELLSAESKSQDTSQITLKTNREKEQSQDLVSEPTTELADTDAAASMA
 NTGSQDATOKSASLPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGIDPAHOSMRISDVSTAKVSKEDMLA
 RQKAAGINYGSWINDKVFVAFNHYVENSNDNIKENQFEDFDEOWENFEDAEAPKAIKHHKKIYRPOSTQAPKET
 VIKTEETDGSHDIDWTQTTDDDTKYESHGMHVGTGIVAGNSKEAAATGERFLGIAPAEAQMFMRFVFANDIMGSAE
 50 SLFIKAIEDAVALGADVINSLSLTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSHDHDPPLATNPD
 YGLVGSPSTGRTPTSVAAINSKWIQLRMLTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
 STDAGYNAQDVKGKIALERDPNKTYDEMIALAKKHGALGVLFNNKPGQSNRSMRLTANGMGIPLSAFISHF
 GKMASQNLNGNTGTSLEFDVSVSKAPSQKGNEHMHSFNWLGSQDGLKPDITAPGGDIYSTYNDNHGSQTGTS
 MASPFQIAGASLLVKQYLEKTPQNLPKEKIADIVKNLLMSNAQIHVNPEKTTTSPRQQGAGLLNIDGAVTSGL
 55 3.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes
- > Spy0416A-1 / Schmitz 1/7 (serotype 4); SEQ ID NO: 90
 60 ADELTTSEPTITNHAQQQAQHLTNTELLSAESKSQSPDTSQITPKTNREKEQPQGLVSEPTTELADTDAAASMA
 NTGPDAQKSASLPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGIDPAHOSMRISDVSTAKVSKEDMLA

- RQKAAGINYGSWINDKVVFAHNYVENDNIKENQGDFDEDWENFEFDAEPAIKKKIYRPOSTQAPKETVI
KTEADTGSHDIDWTQDDDTKYESHGMHTVGIAPEAQVMFMRVFANDVMGSAESL
FIKAIEDAVALGADVINSLLGTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSDDHDPPLATNPDY
LVGSPSTGRPTSVAAINSKWVQLRMLTAKENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYKEST
5 DAGYKAQDVKGKIALIERDPNKTYDEMIALAKKHGALGLVIFNNKPGQSNRSMRLTANGMGIPEAFISHEFGK
AMSQLNGNTGSLEFDSSVSKAPSQKGNEHMNFHSNWGLTSDGALKPDITAPGGDIYSTYNDNHYSQTGTSMA
SPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLLMSNAQIHVNPETKTTSPRQQGA
- > Spy0416A-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 91
10 ADELTTTSEPTITNHAQQQAPLNTELSSAESQSPQDTQVTPETREKEQPOGLVSEPTTTELADTDAAPMA
NTGSPDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGDIDPAHOSMRISDVSTAVKSKEDEMLA
RQKAAGINYGSWINDKVVFAHNYVENDNIKENQFEDFDEDWENFEFDAEAEPAIKKKIYRPOSTQAPKET
VIKTEETDGSHDIDWTQDDDTKYESHGMHTVGIAPEAQVMFMRVFANDVMGSAE
15 SLFIKAIEDAVALGADVINSLLGTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSDDHDPPLATNP
YGLVSPSTGRPTSVAAINSKWVQLRMLTAKENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYKVE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGLVIFNNKPGQSNRSMRLTANGMGIPEAFISHEF
GKAMSQLNGNTGSLEFDSSVSKAPSQKGNEHMNFHSNWGLTSDGALKPDITAPGGDIYSTYNDNHYSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLLMSNAQIHVNPETKTTSPRQQGA
- > Spy0416A-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 92
20 ADELTTTSEPTITNHAQQQAPLNTELSSAESQSPQDTQVTPETREKEQPOGLVSEPTTTELADTDAAPMA
NTGSPDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGDIDPAHOSMRISDVSTAVKSKEDEMLA
RQKAAGINYGSWINDKVVFAHNYVENDNIKENQFEDFDEDWENFEFDAEAEPAIKKKIYRPOSTQAPKET
VIKTEETDGSHDIDWTQDDDTKYESHGMHTVGIAPEAQVMFMRVFANDVMGSAE
25 SLFIKAIEDAVALGADVINSLLGTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSDDHDPPLATNP
YGLVSPSTGRPTSVAAINSKWVQLRMLTAKENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYKVE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGLVIFNNKPGQSNRSMRLTANGMGIPEAFISHEF
GKAMSQLNGNTGSLEFDSSVSKAPSQKGNEHMNFHSNWGLTSDGALKPDITAPGGDIYSTYNDNHYSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLLMSNAQIHVNPETKTTSPRQQGA
- > Spy0416A-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 93
30 ADELTTTSEPTITNHAQQQAPLNTELSSAESQSPQDTQVTPETREKEQPOGLVSEPTTTELADTDAAPMA
NTGSPDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGDIDPAHOSMRISDVSTAVKSKEDEMLA
RQKAAGINYGSWINDKVVFAHNYVENDNIKENQFEDFDEDWENFEFDAEAEPAIKKKIYRPOSTQAPKET
VIKTEETDGSHDIDWTQDDDTKYESHGMHTVGIAPEAQVMFMRVFANDVMGSAE
35 SLFIKAIEDAVALGADVINSLLGTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSDDHDPPLATNP
YGLVSPSTGRPTSVAAINSKWVQLRMLTAKENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYKVE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGLVIFNNKPGQSNRSMRLTANGMGIPEAFISHEF
GKAMSQLNGNTGSLEFDSSVSKAPSQKGNEHMNFHSNWGLTSDGALKPDITAPGGDIYSTYNDNHYSQTGTS
40 MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLLMSNAQIHVNPETKTTSPRQQGA
- > Spy0416A-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 94
45 ADELSTMSEPTITNHAQQQAHLTNTELSSAESKSQDTQSLTAKNRKEQSQDLVSEPTTTELADTDAASMA
NTGSPDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGDIDPAHOSMRISDVSTAVKSKEDEMLA
RQKAAGINYGSWINDKVVFAHNYVENDNIKENQFEDFDEDWENFEFDAEAEPAIKKKIYRPOSTQAPKET
VIKTEETDGSHDIDWTQDDDTKYESHGMHTVGIAPEAQVMFMRVFANDVMGSAE
50 SLFIKAIEDAVALGADVINSLLGTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSDDHDPPLATNP
YGLVSPSTGRPTSVAAINSKWVQLRMLTAKENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYKVE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGLVIFNNKPGQSNRSMRLTANGMGIPEAFISHEF
GKAMSQLNGNTGSLEFDSSVSKAPSQKGNEHMNFHSNWGLTSDGALKPDITAPGGDIYSTYNDNHYSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLLMSNAQIHVNPETKTTSPRQQGA
- > Spy0416A-1 / Schmitz 1/253 (serotype 49); SEQ ID NO: 95
55 ADELTTTSEPTITNHAQQQAOPLNTELSSAESQSPDISQVTPETREKEQPOGLVSEPTTTELADTDAAPMA
NTGSPDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQGKVVAVIDTGDIDPAHOSMRISDVSTAVKSKEDEMLA
RQKAAGINYGSWINDKVVFAHNYVENDNIKENQFEDFDEDWENFEFDAEAEPAIKKKIYRPOSTQAPKET
VIKTEETDGSHDIDWTQDDDTKYESHGMHTVGIAPEAQVMFMRVFANDVMGSAE
60 SLFIKAIEDAVALGADVINSLLGTANGAQLSGSKPLMEAIEKAKKAGVSVVAAGNERVYGSDDHDPPLATNP
YGLVSPSTGRPTSVAAINSKWVQLRMLTAKENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYKVE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGLVIFNNKPGQSNRSMRLTANGMGIPEAFISHEF
GKAMSQLNGNTGSLEFDSSVSKAPSQKGNEHMNFHSNWGLTSDGALKPDITAPGGDIYSTYNDNHYSQTGTS

GKAMSQLNGNGTGSLEFDSSVSKAPSQKGNEENNHSFSNWLTSOGYLPDITAPGGDIYSTYNDNHYSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLMSNAQIHVNPFETKTTSPRQQGA

> Spy0416A-1 / Schmitz 1/14 (serotype 6); SEQ ID NO: 96

5 ADELTTTSEPTITNHAQQQAQHNTTEELSSAESKPQDTSQITLPKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGPDATQKSASLPPVNTVDHWVKTGAWDKGYKGQGVKVAVIDTGDIDPAHQSMRISDVSTAKVSKSEDMLA
RQKAAGINYGSWINDKVVFHHNYVENSNDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQDDDTKYESHGMHTGIVAGNSKEAAATGERFLGIAPEAQVMFMVRVANDVMGSAE
10 SLFIKAIEDAVALGADVINLSLTGANTQAQLSGSKPLMEAIEKAKKAGVSVVAAAGNERVYGSDDHDPLATNPD
YGLVGSPTGRPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYESVDFKNIKDSLGYDKSHQFAYVKE
STDAGYKAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLFNNKPGQSNRSMRLTANGMGIPIASFISHEF
GKAMSQLNGNGTGSLEFDSSVSKAPSQKGNEENNHSFSNWLTSOGYLPDITAPGGDIYSTYNDNHYSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLMSNAQIHVNPFETKTTSPRQQGA

15 > Spy0416A-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 97

ADELTTTSEPTITNHAQQQAQHNTTEELSSAESKPQDTSQITLPKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGPDATQKSASLPPVNTVDHWVKTGAWDKGYKGQGVKVAVIDTGDIDPAHQSMRISDVSTAKVSKSEDMLA
RQKAAGINYGSWINDKVVFHHNYVENSNDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQDDDTKYESHGMHTGIVAGNSKEAAATGERFLGIAPEAQVMFMVRVANDVMGSAE
20 SLFIKAIEDAVALGADVINLSLTGANTQAQLSGSKPLMEAIEKAKKAGVSVVAAAGNERVYGSDDHDPLATNPD
YGLVGSPTGRPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYESVDFKNIKDSLGYDKSHQFAYVKE
STDAGYKAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLFNNKPGQSNRSMRLTANGMGIPIASFISHEF
GKAMSQLNGNGTGSLEFDSSVSKAPSQKGNEENNHSFSNWLTSOGYLPDITAPGGDIYSTYNDNHYSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLMSNAQIHVNPFETKTTSPRQQGA

25

> Spy0416A-1 / Schmitz 1/234 (serotype 44); SEQ ID NO: 98

ADELTTTSEPTITNHAQQQAQHNTTEELSSAESKPQDTSQITLPKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGPDATQKSASLPPVNTVDHWVKTGAWDKGYKGQGVKVAVIDTGDIDPAHQSMRISDVSTAKVSKSEDMLA
RQKAAGINYGSWINDKVVFHHNYVENSNDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHHKIYRPQSTQAPKET
30 VIKTEETDGSHDIDWTQDDDTKYESHGMHTGIVAGNSKEAAATGERFLGIAPEAQVMFMVRVANDVMGSAE
SLFIKAIEDAVALGADVINLSLTGANTQAQLSGSKPLMEAIEKAKKAGVSVVAAAGNERVYGSDDHDPLATNPD
YGLVGSPTGRPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYKAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLFNNKPGQSNRSMRLTANGMGIPIASFISHEF
GKAMSQLNGNGTGSLEFDSSVSKAPSQKGNEENNHSFSNWLTSOGYLPDITAPGGDIYSTYNDNHYSQTGTS
35 MASPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLMSNAQIHVNPFETKTTSPRQQGA

> Spy0416A-1 / Schmitz 1/22 (serotype 4); SEQ ID NO: 99

ADELTTTSEPTITNHAQQQAQHNTTEELSSAESKPQDTSQITLPKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGPDATQKSASLPPVNTVDHWVKTGAWDKGYKGQGVKVAVIDTGDIDPAHQSMRISDVSTAKVSKSEDMLA
40 RQKAAGINYGSWINDKVVFHHNYVENSNDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHHKIYRPQSTQAPKETVI
KTEETDGSHDIDWTQDDDTKYESHGMHTGIVAGNSKEAAATGERFLGIAPEAQVMFMVRVANDVMGSAE
SLFIKAIEDAVALGADVINLSLTGANTQAQLSGSKPLMEAIEKAKKAGVSVVAAAGNERVYGSDDHDPLATNPDYG
LVGSPTGRPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYESVDFKDIKDSLGYDKSHQFAYVKE
45 DAGYKAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLFNNKPGQSNRSMRLTANGMGIPIASFISHEFGK
AMSQLNGNGTGSLEFDSSVSKAPSQKGNEENNHSFSNWLTSOGYLPDITAPGGDIYSTYNDNHYSQTGTSMA
SPQIAGASLLVKQYLEKTQPNLPEKEIADIVKNLMSNAQIHVNPFETKTTSPRQQGA

3.4 Antigenic fragment Spy0416A-6

50 > Spy0416A-6 / SF370 (serotype 1); SEQ ID NO: 5

AVIDTGDIDPAHQSMRISDVSTAKVSKSEDMLARQKAAGINYGSWINDKVVFHHNYVENSNDNIKENQFEDFDED
WENFEFDAEAEPKAIKKHHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQDDDTKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMVRVANDVMGSAEESLFIKAIEDAVALGADVINLSLTGANTQAQLSGSKPLMEAIE
55 KAKKAGVSVVAAAGNERVYGSDDHDPLATNPDYG LVGSPTGRPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYESVDFKDIKDSL

3.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-6 / Schmitz 1/7 (serotype 4); SEQ ID NO: 100

60 AVIDTGDIDPAHQSMRISDVSTAKVSKSEDMLARQKAAGINYGSWINDKVVFHHNYVENSNDNIKENQFEDFDED

WENFEFDAEPAKAIKKNKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKEAA
ATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIEKA
KKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTAKELENRADLNHG
KAIYSESVDFKDIKDSL

5 > Spy0416A-6 / Schmitz 1/39 (serotype 12); SEQ ID NO: 101
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED
WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE

10 KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/55 (serotype 118); SEQ ID NO: 102
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED

15 WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE
KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

20 > Spy0416A-6 / Schmitz 1/56 (serotype 28); SEQ ID NO: 103
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED
WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE
KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN

25 KAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/94 (serotype 1); SEQ ID NO: 104
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED
WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE

30 KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/253 (serotype 49); SEQ ID NO: 105
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED
WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE
KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKGLENRADLN
HGKAIYSESVDFKDIKDSL

40 > Spy0416A-6 / Schmitz 1/174 (serotype 6); SEQ ID NO: 106
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED
WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE
KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKNIKDSL

50 > Spy0416A-6 / Schmitz 1/176 (serotype 83); SEQ ID NO: 107
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED
WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE
KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKNIKDSL

55 > Spy0416A-6 / Schmitz 1/234 (serotype 44); SEQ ID NO: 108
AVIDTGDPAHQSMRISDVSTAKVSKSEDMALARQKAAGINNGSWINDKVVFAHNHYVENSNDNIKENQFEDFDED
WENFEFDAEAEPAKAIKKHKIYRPOSTQAPKETV1KTEETDGSHIDWTQTDDETKYESHGMHTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSQLGTANGAQLSGSKPLMEAIE
KAKKAGGVSVVVAAGNERVYGSDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN

60 HGKAIYSESVDFKNIKDSL

> Spy0416A-6 / Schmitz 1/22 (serotype 4); SEQ ID NO: 109
 AVIDTGDPAHQSMRISDVSTAKVSKEDMLAROKAAGINYGSWINDKVFVFAHNHYVENSNDNIKENQFGDFDED
 WENFENFDÄEPAKAIKKHHKIYRPQSTQAPKETVIKTEETDGSHIDIWTDQTDDDTKYESGMHVTGIVAGNSKEA
 5 ATGERFLGIAPAEQVMFMRVFANDVMSAESLFIKAIEDAVALGADVINLSLTANGAQLSGSKPLMEAIEKA
 KRAKAGVSVVAAAGNERVYGSDDHDPPLATNPDYGLVGSPTGRPTSVAAINSKWVIQRMLTAKELENRADLNHG
 KAIYESVDFKD1KDSL

3.6 Antigenic fragment Spy0416A-7

> Spy0416A-7 / SF370 (serotype 1); SEQ ID NO: 6
 SQITLKNREKEQSQDVLSEPTTTELADTDAAASMANTGSATQKSASLPPVNTDVHDWVTKKGAWDKGYKGQG
 KVVAVIDTGDPAHQSMRISDVSTAKVSKEDMLAROKAAGINYGSWINDKVFVFAHNHYVENSNDNIKENQFGDF
 10 DEDWENFEFDAEAEPAKAIKKHHKIYRPQSTQAPKETVIKTEETDGSHIDIWTDQTDDDTKYESGMHVTGIVAGN
 SKEAAATGERFLGIAPAEQVMFMRVFANDVMSAESLFIKAIEDAVALGADVINLSLTANGAQLSGSKPLMEA
 15 AIEKAKAGVSVVAAAGNERVYGSDDHDPPLATNPDYGLVGSPTGRPTSVAAINSKWVIQRMLTAKELENRADL
 DLNHGKAIYESVDFKD1KDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
 LGVLIFNNKPGQSNRSRMLTANGMGIPIAFISHFGKAMSQLNGNGTGS

20 3.7 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-7 / Schmitz 1/7 (serotype 4); SEQ ID NO: 110
 SQITPKTNREKEQPQGLVSEPTTTELADTDAAASMANTGPDATQKSASLPPVNTDVHDWVTKKGAWDKGYKGQG
 KVVAVIDTGDPAHQSMRISDVSTAKVSKEDMLAROKAAGINYGSWINDKVFVFAHNHYVENSNDNIKENQFGDF
 25 DEDWENFEFDAEAEPAKAIKKHHKIYRPQSTQAPKETVIKTEETDGSHIDIWTDQTDDDTKYESGMHVTGIVAGN
 EAAATGERFLGIAPAEQVMFMRVFANDVMSAESLFIKAIEDAVALGADVINLSLTANGAQLSGSKPLMEA
 EAKAKAGVSVVAAAGNERVYGSDDHDPPLATNPDYGLVGSPTGRPTSVAAINSKWVIQRMLTAKELENRADL
 NHGKAIYESVDFKD1KDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
 VLIFNNKPGQSNRSRMLTANGMGIPIAFISHFGKAMSQLNGNGTGS

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> Spy0416A-7 / Schmitz 1/39 (serotype 12); SEQ ID NO: 111
 SQITLKNREKEQPQGLVSEPTTTELADTDAAPMANTGPDATQKSASLPPVNTDVHDWVTKKGAWDKGYKGQG
 KVVAVIDTGDPAHQSMRISDVSTAKVSKEDMLAROKAAGINYGSWINDKVFVFAHNHYVENSNDNIKENQFGDF
 35 DEDWENFEFDAEAEPAKAIKKHHKIYRPQSTQAPKETVIKTEETDGSHIDIWTDQTDDDTKYESGMHVTGIVAGN
 SKEAAATGERFLGIAPAEQVMFMRVFANDVMSAESLFIKAIEDAVALGADVINLSLTANGAQLSGSKPLMEA
 EAKAKAGVSVVAAAGNERVYGSDDHDPPLATNPDYGLVGSPTGRPTSVAAINSKWVIQRMLTAKELENRADL
 DLNHGKAIYESVDFKD1KDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
 LGVLIFNNKPGQSNRSRMLTANGMGIPIAFISHFGKAMSQLNGNGTGS

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> Spy0416A-7 / Schmitz 1/55 (serotype 118); SEQ ID NO: 112
 SQVTPENREKEQPQGLVSEPTTTELADTDAAPMANTGPDATQKSASLPPVNTDVHDWVTKKGAWDKGYKGQG
 KVVAVIDTGDPAHQSMRISDVSTAKVSKEDMLAROKAAGINYGSWINDKVFVFAHNHYVENSNDNIKENQFGDF
 45 DEDWENFEFDAEAEPAKAIKKHHKIYRPQSTQAPKETVIKTEETDGSHIDIWTDQTDDDTKYESGMHVTGIVAGN
 SKEAAATGERFLGIAPETQVMFMRVFANDVMSAESLFIKAIEDAVALGADVINLSLTANGAQLSGSKPLMEA
 EAKAKAGVSVVAAAGNERVYGSDDHDPPLATNPDYGLVGSPTGRPTSVAAINSKWVIQRMLTAKELENRADL
 DLNHGKAIYESVDFKD1KDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
 LGVLIFNNKPGQSNRSRMLTANGMGIPIAFISHFGKAMSQLNGNGTGS

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> Spy0416A-7 / Schmitz 1/56 (serotype 28); SEQ ID NO: 113
 SQITPKTNREKEQPQGLVSEPTTTELADTDAAPMANTGPDATQKSASLPPVNTDVHDWVTKKGAWDKGYKGQG
 KVVAVIDTGDPAHQSMRISDVSTAKVSKEDMLAROKAAGINYGSWINDKVFVFAHNHYVENSNDNIKENQFGDF
 55 DEDWENFEFDAEAEPAKAIKKHHKIYRPQSTQAPKETVIKTEETDGSHIDIWTDQTDDDTKYESGMHVTGIVAGN
 EAAATGERFLGIAPAEQVMFMRVFANDVMSAESLFIKAIEDAVALGADVINLSLTANGAQLSGSKPLMEA
 EAKAKAGVSVVAAAGNERVYGSDDHDPPLATNPDYGLVGSPTGRPTSVAAINSKWVIQRMLTAKELENRADL
 VLIFNNKPGQSNRSRMLTANGMGIPIAFISHFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/94 (serotype 1); SEQ ID NO: 114

SQITLKNREKEQSQDVLSEPTTTELADTDAAASMANTGSATQKSASLPPVNTDVHDWVTKKGAWDKGYKGQG
 KVVAVIDTGDPAHQSMRISDVSTAKVSKEDMLAROKAAGINYGSWINDKVFVFAHNHYVENSNDNIKENQFGDF

- DEDWENFEEFDAEAEPKAIKKHK1YRPQSTQAPKETVIKTEETDGS HDIDWWTQTD DDTKYESGHMHTGVIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFDVMGSAESLFIKAIEDAVALGADVINLSLTGANGAQLSGSKPLME
AIEKAKKAGVS VVAAAGNERVYGS DHDDPLATNPDYGLVGS P STGRPTV SVAI NSKW VI QRLMTVKEL ENRA
DLNHGKAIYSES VDFKD IDKDSL GYDKSHQFAYV KEST DAGYNAQDVKGKIALIERDPNKTYDEMIA LAKKHGA
5 LGVLIFNNKPGQSNRSRMLTANGMG I P S AFISHEFGKAMS QLNGNGTGS
- > Spy0416A-7 / Schmitz 1/253 (serotype 19); SEQ ID NO: 115
SQITPKTNREKEQPGQLVSEPTTTELADTDAAPMANTGP DATQKSASLPPVNTDVHDWVTKGAWDKGYKGQG
KVVAVIDTGIDPAHQS MRISDV STAKVSKEDMLARQKAAG INYGSWINDKVVFAHNYVENSNDNIKENQFEDF
10 DEOWENFEFDAEAEPKAIKKHK1YRPQSTQAPKETVIKTEETDGS HDIDWWTQTD DDTKYESGHMHTGVIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFDVMGSAESLFIKAIEDAVALGADVINLSLTGANGAQLSGSKPLME
AIEKAKKAGVS VVAAAGNERVYGS DHDDPLATNPDYGLVGS P STGRPTV SVAI NSKW VI QRLMTVKEL ENRA
DLNHGKAIYSES VDFKD IDKDSL GYDKSHQFAYV KEST DAGYNAQDVKGKIALIERDPNKTYDEMIA LAKKHGA
LGLLIFNNKPGQSNRSRMLTANGMG I P S AFISHEFGKAMS QLNGNGTGS
- 15 > Spy0416A-7 / Schmitz 1/174 (serotype 6); SEQ ID NO: 116
SQITPKTNREKEQPGQLVSEPTTTELADTDAASMAN TGP DATQKSASLPPVNTDVHDWVTKGAWDKGYKGQG
KVVAVIDTGIDPAHQS MRISDV STAKVSKEDMLARQKAAG INYGSWINDKVVFAHNYVENSNDNIKENQFEDF
DEOWENFEFDAEAEPKAIKKHK1YRPQSTQAPKETVIKTEETDGS HDIDWWTQTD DDTKYESGHMHTGVIVAGN
20 SKEAAATGERFLGIAPEAQVMFMRVFDVMGSAESLFIKAIEDAVALGADVINLSLTGANGAQLSGSKPLME
AIEKAKKAGVS VVAAAGNERVYGS DHDDPLATNPDYGLVGS P STGRPTV SVAI NSKW VI QRLMTVKEL ENRA
DLNHGKAIYSES VDFKD IDKDSL GYDKSHQFAYV KEST DAGYNAQDVKGKIALIERDPNKTYDEMIA LAKKHGA
LGVLIFNNKPGQSNRSRMLTANGMG I P S AFISHEFGKAMS QLNGNGTGS
- 25 > Spy0416A-7 / Schmitz 1/176 (serotype 83); SEQ ID NO: 117
SQITLKTNREKEQPGQLVSEPTTTELADTDAAPMANTGP DATQKSASLPPVNTDVHDWVTKGAWDKGYKGQG
KVVAVIDTGIDPAHQS MRISDV STAKVSKEDMLARQKAAG INYGSWINDKVVFAHNYVENSNDNIKENQFEDF
DEOWENFEFDAEAEPKAIKKHK1YRPQSTQAPKETVIKTEETDGS HDIDWWTQTD DDTKYESGHMHTGVIVAGN
30 SKEAAATGERFLGIAPEAQVMFMRVFDVMGSAESLFIKAIEDAVALGADVINLSLTGANGAQLSGSKPLME
AIEKAKKAGVS VVAAAGNERVYGS DHDDPLATNPDYGLVGS P STGRPTV SVAI NSKW VI QRLMTVKEL ENRA
DLNHGKAIYSES VDFKD IDKDSL GYDKSHQFAYV KEST DAGYNAQDVKGKIALIERDPNKTYDEMIA LAKKHGA
LGVLIFNNKPGQSNRSRMLTANGMG I P S AFISHEFGKAMS QLNGNGTGS
- 35 > Spy0416A-7 / Schmitz 1/234 (serotype 44); SEQ ID NO: 118
SQITPKTNREKEQPGQLVSEPTTTELADTDAASMAN TGDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQG
KVVAVIDTGIDPAHQS MRISDV STAKVSKEDMLARQKAAG INYGSWINDKVVFAHNYVENSNDNIKENQFEDF
DEOWENFEFDAEAEPKAIKKHK1YRPQSTQAPKETVIKTEETDGS HDIDWWTQTD DDTKYESGHMHTGVIVAGN
40 SKEAAATGERFLGIAPEAQVMFMRVFDVMGSAESLFIKAIEDAVALGADVINLSLTGANGAQLSGSKPLME
AIEKAKKAGVS VVAAAGNERVYGS DHDDPLATNPDYGLVGS P STGRPTV SVAI NSKW VI QRLMTVKEL ENRA
DLNHGKAIYSES VDFKD IDKDSL GYDKSHQFAYV KEST DAGYNAQDVKGKIALIERDPNKTYDEMIA LAKKHGA
LGVLIFNNKPGQSNRSRMLTANGMG I P S AFISHEFGKAMS QLNGNGTGS
- > Spy0416A-7 / Schmitz 1/22 (serotype 4); SEQ ID NO: 119
SQITPKTNREKEQPGQLVSEPTTTELADTDAASMAN TGDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQG
45 KVVAVIDTGIDPAHQS MRISDV STAKVSKEDMLARQKAAG INYGSWINDKVVFAHNYVENSNDNIKENQFDF
DEOWENFEFDAEAEPKAIKKHK1YRPQSTQAPKETVIKTEETDGS HDIDWWTQTD DDTKYESGHMHTGVIVAGNSK
EAAATGERFLGIAPEAQVMFMRVFDVMGSAESLFIKAIEDAVALGADVINLSLTGANGAQLSGSKPLMEAI
EKAKKAGVS VVAAAGNERVYGS DHDDPLATNPDYGLVGS P STGRPTV SVAI NSKW VI QRLMTVKEL ENRADL
NHGKAIYSES VDFKD IDKDSL GYDKSHQFAYV KEST DAGYNAQDVKGKIALIERDPNKTYDEMIA LAKKHGA
LGVLIFNNKPGQSNRSRMLTANGMG I P S AFISHEFGKAMS QLNGNGTGS
- 50 > Spy0416A-7 / Schmitz 1/22 (serotype 4); SEQ ID NO: 119
SQITPKTNREKEQPGQLVSEPTTTELADTDAASMAN TGDATQKSASLPPVNTDVHDWVTKGAWDKGYKGQG
KVVAVIDTGIDPAHQS MRISDV STAKVSKEDMLARQKAAG INYGSWINDKVVFAHNYVENSNDNIKENQFDF
DEOWENFEFDAEAEPKAIKKHK1YRPQSTQAPKETVIKTEETDGS HDIDWWTQTD DDTKYESGHMHTGVIVAGNSK
EAAATGERFLGIAPEAQVMFMRVFDVMGSAESLFIKAIEDAVALGADVINLSLTGANGAQLSGSKPLMEAI
EKAKKAGVS VVAAAGNERVYGS DHDDPLATNPDYGLVGS P STGRPTV SVAI NSKW VI QRLMTVKEL ENRADL
NHGKAIYSES VDFKD IDKDSL GYDKSHQFAYV KEST DAGYNAQDVKGKIALIERDPNKTYDEMIA LAKKHGA
LGVLIFNNKPGQSNRSRMLTANGMG I P S AFISHEFGKAMS QLNGNGTGS
- 3.8 Full length Spy0416B**
- > Spy0416B / SF370 (serotype 1); SEQ ID NO: 56
HVDFQKGRFTLTSHSILKTYQGGEVTV PANGKVTVRV TMDVQS QFTKELTKQMPNGYYLEG FVRFRDSQDDQLNR
55 VNIPVFGKGFQFENLA VAEESIYRLKSGQKGTGFYFDESGPKD YI V GKHTGLVTLGSETNVSTKTISDNLH
TLGTFKNADGKFLIKE NQGNPV LAI SPQDNQDFAAFKGVFLRQYQGLKASVY HASDEKHNPLWVSPESE
KGDKNFNSDIRFAKSTTLLGTA FSGKSLTGAELPDGHYH YVSYSPDVGAKRQEMT FDMILDROKPVLSQAT
FDPETRNFKPPEPLKDRGLAGVRKDSVYFLERKDKNPKY TINDS QYV SVEDNKT FVERQADGSFLPLDVKAK
LGDFYV MVEDFAGVNAIAKLGHDLPQT LKTP I KLKL TDG NYQ KETLKD NL EM TQS DGT GLV NQ QLAVH
60 NQPQSLTKMNQDF FIS PNE DGKND FV AFKGLKNNVY ND LT VNV YAKDDH QK QTP I WSS QAG ASV SAI EST AW

5 YGITARGSKWMPGDYQVVVTYRDEHGEKHEOKQYTISVNDKPKMITQGRFDTINGVDHFTPDKTKALDSSGIVR
 EEVFYLAKKNRGKFDTEGKGDTIVSDNKVYIPKNPDGSYTISKRDGVTLSDYYLVEDRAGNVSFATLRLK
 AVGDKRAVVFNLGLDPVPEDKQIVNFTYLRDADGKPIENLEYNNNSGNSLILPYGRKYTVELLYTDNTAAKLE
 SDKIVSETLSADNNFQQTFTKIMTATSQITTAHDHLLPEGSRVSLSKTAQDQLPLEQSILYVVPKAYGKTQVEG
 10 TYEVVVSLPKGYRIEGNTKVNTLPNEVHELSLRVLVKVGDASTDGTGDHKVMSKNNSQALTASATPTKSTSATA
 KALPST

4. Spy0872

10 4.1 Full length Spy0872

> Spy0872 / SF370 (serotype 1); SEQ ID NO: 120
 DQDVQFLGVNDFHGALDNTGTYATPFSKIPNAGTAAQALGAYMDAIEFKQANQDGTSIRVQAGDMVGASPA
 15 NSALQDDEPTVKVNFKMKEFYGTGLNHFEDEGFLDEFNRIMTQGAPDFESTINDTQKQEHEASQHTIVIANVI
 DVKTKDIPYGWKPYAIKDIAINDKIVKIGFIGVVTTEIPIVLVKLQNYESHYQFLDVAETIAKYAKELQEQHVHA
 IUVLVRPATSKDGVVNDHEMATMEVKNQYIPBESIDIIFQAGHNHQYTNGTTRIVQALSQGKAYADVRGT
 20 LDTDTNDFIKPTPSANVAVAPGKTEKNTSDIKAIIHNDVKTVERKIGTATNSTISKTENIDKESPVGNL
 ATTAQLTIAKKTFTVDFAMTNNGGIRSDLVVKNDRTITWGAAQAVQFGNILQVIQMTGQHIVDVLNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 NQTYFLQMSGLTYTTDNDPKNSDTPFKIVKVKVYQDNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 25 VYKDNGEEINLTTTYYTVVNDFLYGGGGDGSFAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
 VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEVISDLTSTENTNNSLGKETTNKNNTISSTLPIT

4.2 Antigenic fragment Spy0872-2

> Spy0872-2 / SF370 (serotype 1); SEQ ID NO: 7
 AIIINHANDIVKVTVERKIGTATNSTISKTENIDKESPVGNLATTAAQLTIAKKTFTVDFAMTNNGGIRSDLV
 VKNDRTITWGAAQAVQFGNILQVIQMTGQHIVDVLNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 30 VYKDNGEEINLTTTYYTVVNDFLYGGGGDGSFAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
 VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEVISDLTSTENTNNSLGKETTNKNNTISSTLPIT

4.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0872-2 / Schmitz 1/7 (serotype 4); SEQ ID NO: 121
 AIIINHANDIVKVTVERKIGTATNSTISKTENIDKESPVGNLVTAAQLTIAKKTFTVDFAMTNNGGIRSDLV
 35 VKNDRTITWEEAAQAVQFGNILQVIQMTGQHIVDVLNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 VYKDNGEEINLTTTYYTVVNDFLYGGGGDGSFAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
 VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEIIISDLTSTENTNNSLGKETTNKNNTISSTLPIT

> Spy0872-2 / Schmitz 1/39 (serotype 12); SEQ ID NO: 122
 AIIINHANDIVKVTVERKIGTATNSTISKTENIDKESPVGNLVTAAQLTIAKKTFTVDFAMTNNGGIRSDLV
 VKNDRTITWGAAQAVQFGNILQVIQMTGQHIVDVLNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 40 VYKDNGEEINLTTTYYTVVNDFLYGGGGDGSFAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
 VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEVISDLTSTENTNNSLGKETTNKNNTISSTLPIT

> Spy0872-2 / Schmitz 1/55 (serotype 118); SEQ ID NO: 123
 AIIINHANDIVKVTVERKIGTATNSTISKTENIDKESPVGNLVTAAQLTIAKKTFTVDFAMTNNGGIRSDLV
 VKNDRTITWGAAQAVQFGNILQVIQMTGQHIVDVLNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 45 VYKDNGEEINLTTTYYTVVNDFLYGGGGDGSFAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
 VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEVISDLTSTENTNNSLGKETTNKNNTISSTLPIT

> Spy0872-2 / Schmitz 1/56 (serotype 28); SEQ ID NO: 124
 AIIINHANDIVKVTVERKIGTATNSTISKTENIDKESPVGNLVTAAQLTIAKKTFTVDFAMTNNGGIRSDLV
 VKNDRTITWGAAQAVQFGNILQVIQMTGQHIVDVLNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 50 VYKDNGEEINLTTTYYTVVNDFLYGGGGDGSFAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
 VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEIIISDLTSTENTNNSLGKETTNKNNTISSTLPIT

> Spy0872-2 / Schmitz 1/94 (serotype 1); SEQ ID NO: 125
 AIIINHANDIVKVTVERKIGTATNSTISKTENIDKESPVGNLVTAAQLTIAKKTFTVDFAMTNNGGIRSDLV
 VKNDRTITWGAAQAVQFGNILQVIQMTGQHIVDVLNQYDENQTYFLQMSGLTYTTDNDPKNSDTPFKIVK
 55 VYKDNGEEINLTTTYYTVVNDFLYGGGGDGSFAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
 VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEVISDLTSTENTNNSLGKETTNKNNTISSTLPIT

VTSNLESSTKVNSAGKHSIISKVFRNRDGNVSSVISDLLTSTENTNNSLGKKETTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/253 (serotype 49); SEQ ID NO: 126

AIIHANDIVKVTTERKIGTATNSTSISKTENIDKESPGVNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPGFNGILQVIQMTGQHIIYDVLNQQYDENQTFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYYTVVNVDFLYGGDDGFSAFKKAKLIGAINDTDEAFTITYITNLQASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNVSSVISDLLTSTENTNNSLGKKETTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/176 (serotype 83); SEQ ID NO: 127

AIIHANDIVKVTTERKIGTATNSTSISKTENIDKESPGVNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPGFNGILQVIQMTGQHIIYDVLNQQYDENQTFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYYTVVNVDFLYGGDDGFSAFKKAKLIGAINDTDEAFTITYITNLQASGKTVNATIKGVKNY
VTSNLERSTKINSAGKHSIISKVFRNRDGNVSSVISDLLTSTENTNNSLGKKETTNKNTISSSTLPIT

15 > Spy0872-2 / Schmitz 1/177 (serotype 22); SEQ ID NO: 128

AIIHANDIVKVTTERKIGTATNSTSISKTENIDKESPGVNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPGFNGILQVIQMTGQHIIYDVLNQQYDENQTFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYYTVVNVDFLYGGDDGFSAFKKAKLIGAINDTDEAFTITYITNLQASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNVSSVISDLLTSTENTNNSLGKKETTNKNTISSSTLPIT

20 > Spy0872-2 / Schmitz 1/234 (serotype 4); SEQ ID NO: 129

AIIHANDIVKVTTERKIGTATNSTSISKTENIDKESPGVNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPGFNGILQVIQMTGQHIIYDVLNQQYDENQTFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYYTVVNVDFLYGGDDGFSAFKKAKLIGAINDTDEAFTITYITNLQASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNVSSVISDLLTSTENTNNSLGKKETTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/22 (serotype 4); SEQ ID NO: 130

AIIHANDIVKVTTERKIGTATNSTSISKTENIDKESPGVNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWEAAQAVQPGFNGILQVIQMTGQHIIYDVLNQQYDENQTFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYYTVVNVDFLYGGDDGFSAFKKAKLIGAINDTDEAFTITYITNLQASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNVSSVISDLLTSTENTNNSLGKKETTNKNTISSSTLPIT

5. Further Sequences

35 > Spy0488 / SF370 (serotype 1); SEQ ID NO: 8

LRIQISRLIIDVLELAFGVGKEETTSQSFDQSPPQVVLRYRGEANTVRFAYTNQMSLMKDIRIALDGSDKSLT
AQIPGMGHVYECFGTSRAGIFTMSGVPESTPVANPNVQTKYIRYFKVIDDMHNTMYKGTFLVQPQAWKYT
MKSVDOLPVDDLNHIGVAGIERMTTLKNCAGALLTTGGSAFPDNKIVKSINPKGRQATITYGDGSTDIIIPPV
LWKGSKVKEPEADQSVPGTPTPGKPFKRQDSLNEHAMVNVEPLSHVVKDNKIVIDEKSTGRFEPFRPNED
40 EKEKPASDVKVRPAEVGWSALAPLSVMAESDRLKS

> Spy0895 / SF370 (serotype 1); SEQ ID NO: 9

TNNQTDILLDVYAYNHAFRIAKALPNIPKTALEYMLKERRELNLAFLEAHAAENRTIEDQYHCSLWLNS
LEDEQIANYLIDLEVKGKNGAIIDFVRSVSPILYRFLTESEIPNFKAYIFDTKNDQYDTHFQAMLESDH
45 EVFKAYSLQKSRNVTTSKLADMILTSLTSEPOIEKLDFLVLRFHEKAVERNPLAHLIKPFDDEELHRTTHFSSQA
FLENITLATFSGVYIRREPFYFDDMNAIIKKELSLWRQSIV

> Spy1536 / SF370 (serotype 1); SEQ ID NO: 131

IEMFGGAYDIRTVLQVNKGKEDKRKGAYQFVAVGISRASLAAQLLYWA1TPFTESTAEDTTGGYSDADFLRINO
50 FYMETSQNAAIYQALSILAGKFVTLIDYKGVYLVLDVNNESTFKGTLLHADTVTGVNKGQFTSSAELIDYVSHLKL
GDEVTVQFTSDNPKPKVGRIIKLKNKGNGKNG1GALTDTHSVNSDTEV1STKGVGGPSAGLMTLDIYDQ1'K
EDLRKGRTIAGTGTIGKDGEGWDIGGAGLKVVAAEAGADIFFVPPNPVDKEIKKVNPNNAISNYEEAKRAAKR
LKTCKMIVPVTTVQEALVYLRK

55 > Spy1666 / SF370 (serotype 1); SEQ ID NO: 132

TKEFHHTVLLHETVMDLDIKPDCIYVDAFLGGSCHSAYLLSKLGEHHYCFDQQDKAIDNAQVTLKSYIDK
GQVTFKIDNFRHLKARLTALGVDEIDGILYDGLVSSPQLDERERGFSYKQDAPLDMRMDRQSLTAYEVNTY
PFNDFLWIFFKYGEDFKSKQTAKEQARA1KPIETTTELAElikAAKPAKELKKKGHPAKQ1FQAIRIEVND
60 ELGAADES1QDAMELLADLGRISVITFHSLEDRLTQKLFKEASTDVPKGPLPLIPEDMKPKFELVSRKPILPS
HSELANKRAHSAKLRAVAKKIRK

> SpyI727 / SF370 (serotype 1); SEQ ID NO: 10
 VTTTEQEILTLPRLRGKSGKAYKGTYPNGEVFIKLNTTPIPALAKEQIAQPQLLWAKRMGNQDMMSAQEWLNG
 RTLTKEDMNSKQIIHILLRHLHSKSKLVLNQOLQNYKIEPNYDLYLWDFEONQALPQLIQONNSYLQOIAVKELKRSLP
 5 EFKSEVATIVHGDIKHSNNWVITSGMFILFLWDWSVRLTDORMDVAYLLSHYIPRSRWSEWLSSYYGYKNNDKVM
 QKIIWYGQFSHLTQILKCFDKDRMEHVNQEYIALRKFREIFRKK

SEQUENCE DATA FOR DNA SEQUENCES

1. Spy0269

10 1.1 Full length Spy0269

> Spy0269 / SF370 (serotype 1); SEQ ID NO: 133
 ATGGACTTAGAACACAAAGCAGGCCAACCAAGTTAACGAGAAAATTGCTTAACTCAAACAATTGCTTTATTGA
 15 GTGCCAGTGTAGCGCTATCTCACCAAGTCAGAGCATGATAGAGCCTCAGGAGAACGAGGCAGTAATAC
 TCACAGCATGATGTTACCAAAGCCAGAACCTAAAGGAGCCAAAGGCAACTATTGATGCTGAGTTGAGA
 CTCAGTCACAAAAAAAGCAGAACACTGAGACAGCTTGACCCCTGCAACAAAATACTGCTGAATAACCAACT
 TAAAAGAGCAGCAAGATAATGAACAAAAAGCTTAAACCTCTGACAAAGAAATTACACTAATACTCTTGCAAG
 20 TAGTGGAGGAGCCTATAGCGAACAGGCCAACATTAACAGAGAGTTAACGCTACTGAACAGAGCTTCAT
 AATGCTCAAGCAGTCAACATTCAAAAGGACTGTCTGTGAGAACAAAATAGCTAACGCTCAATGCTATTGATTAG
 CTCGAGCTCAAGGTTAGTGGAAACAGTCACAAAGCTGTCAGAACAAAATATTGCTTAAGGCTCAATGCTATTGAG
 25 CAATCTCTGATGCTATCATAACAGGCTAACAGGCTTAACAGGCTAATGATAACAAAAGCATTGACTGAAGCTCAGA
 AAGGCTAAAGCTGACTTAAAGCTAAAGGCTAAAGGCTAAAGGCTAATGACTGAAGAGTTGGCAGCTCAGA
 AAGCTCTCTAGCAGAAAAGGAGGAGCAGAACCTAGTCTGTTAACTCTCAGCTCCGTACTCAAGATAGCAT
 30 TGTTGGGATTAACCATGAAAGCACCGCAAGCTTACCTCTGAGAACACTTAAAGGACTTAAAGGACTTAA
 TATATTGGATCAGCTAGTTACATAATTACAAAGGAGCATGAGATCAATTATTGCCAACAGTCTAGTCAG
 GTAACTAACTTAAACATACCAAGGATATTCCAGCAGATCTGAATCAGCTTGTGATCCGGATAATTGGACACC
 AGAAGTGCAAAATGAGCTAGCGCAGTTGCAGCTCATGATTAATGACTGTAGAAGACATAATTGGCTTACCA
 35 CCAGTTACTGTACAGCAGGATCACAGAACATTGCAAGATTAACGAGTACTTACCGCTATAAGAAAATCATGGTA
 ATACAGAACCCATTCTGGCTACCGCAGGGTATCAGGGCATTATGGCTTGGGCTCATGATAAACAC
 TATATTGGAGACTCTGGCCGGCAGGCTCAGGCTCATGGCTTACCGGAAATGATGAAACATGTACGGAGAATTC
 40 TTAAAGGATGTGCTACTGTGATGTTAAACGTGTTATTATGACAGTATCAAGTATATGCTTTACAG
 ATCATTTACAGGAAATACATACCGCCGCTCTAACTTACAGGCTTACATTAACCTTACGGTATGGCTTAC
 TGTTTACCTGGGATTTCACCGCAAGTGTAGGATCTTGAATGAACTTGTGATATTGCTTACAG
 45 ATTGCTAACCATCACGCTTAAAGACCCCTATAAGGCCGTTGGAGATCAGGAAATTATGCCCCAAAGAG
 TAGGACTGTATCTGACTTACAGCAGCAGCAAGGAAAGTAAAGGCTCATGGAGATTAACCTTACGGTATGGCT
 TCACTAACAGAGCTGATATTGGCAGGCTTACAGGCTCATGGCTTACAGGCTTACGGTATGGCTTAC
 50 AAGCAGCTCAGCAGCTTAAATCTCAAGTGGACAACTTAAGTATACTAAAGGTTCTTGAGAACAGAAATTAC
 TAGCAGCTAACAGGAAACAGAACACTGAGCAAGCTACTGGCTGATCAATCATTGACTGAGCTCATGGTGA
 AGCCGACTGACCCAGCACAGGCTTACGGAGCAGCAGCCAGCAGCTGGGCTATGGCTTAC
 GCTCATTGCAATATCTAACGGGACTTTAAATTGATTAACCTCAACCGCTTCAAGTGTATACGGCCTATGATA
 ATACTAACAGGACTGATTTGGCTTAAACTCATCTTGTGTTAAATGCAACAGAGCTTACGGGCTTAC
 55 TAAACAAAGCAGTCTAGAAGCTACTATGGCTACACAGAACAGGCTTACGGTCTTAAACCTTAGCTAAC
 GAAAGGAAATATGGCAGCTTACGGAGAATATGGCTACTGAGCTGATTTGCTGATGGCTTACCTCTAAC
 GCGTAAACCGCTTACATATAGTAGATGACTACTCCGCTTGTGCTTCAAGAAATGGTTAAAAGAACGAA
 ACTATTAGAAGCTTACGGCAAGATTTAGCTGCTGAAATAACAGTCTTGTGAGCAGAACGGCTTGGCCAA
 ACCCTCTGCAACAGAAATTACACTAATACTCTTCAAGTGTAGGAGACCTTATGGCCAAAGGAGCGAAC
 TCTGTGAAATGCTGCAAGATTAACGCTACTGAAACAGAGCTTACATATGCTCAAGCAGATCAACATT
 CTTATGGCTCAGGATCTTACACAGCACATCTTCTGATGAAAGTACTCAAAGAGCTTCA
 AGCAGCAGTCTGATGTGGCAGCTGCGGCTCACAGGATTAGTGGCTAAGGAATCTAAGTGA
 1.2 Antigenic fragment Spy0269-1

> Spy0269-1 / SF370 (serotype 1); SEQ ID NO: 11
 GATGATAGAGCCTCAGGAGAACGAGGAGTAATCTACGAGCATGAGTTACCAAAACAGAACAACTT
 55 AAGAGGCAAAGGCAACTTATGATGCTAGTGAACAAAATCTCAGTCACAAAAAAAGCAGAACCTGACAGAGCTTG
 TACCGCTCTGACAAAATCTACGCTGAAATCAACCACTTAAAGAGGAGCAGAACATAATGAAACAAAAGCTT
 ACCTCTGCAACAGAAATTACACTAATACTCTTCAAGTGTAGGAGACCTTATGGCCAAAGGAGCGAAC
 ATCAAAGAGGTTAACGCTACTGAAACAGAGCTTACATATGCTCAAGCAGATCAACATTCAAAGAGCTGC
 ATTGTCAGAACAAAAGCTAGCATTTACAGCACAGAACACTCTCGAGCTCAAGATTTAGTGGAA
 CAGCTCAAGGTTAGGTTCCGTAAGGATCTTACAGCTCAAGGTTAGGTTCCGTAAGGATCTTAA

TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAACTCTGATGCTTACATAAGCAGCTCAAACGG
 CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAAAGGCTAACGCTGACTTAGAAAATCAAAAGCTAA
 AGTAAAAAGCATTGACTGAAGAGTTGCCAGCTCAGAACAGCTCTAGCAGAAAAGAGGCAGAACTTAGT
 CGTCCTTAATCCCTCAGCTCGCTACTCAGAAGTACGATTGTGGGATAATACCATGAGCTTACATGTTAAT
 5 ATCCCTCTGAGAACTTAAAAATTAGAAGCTAGTGTGTTATATGGATCAGCTAGTTACATAATATTACAA
 AGAGCATGAGCAGATAAAATTATGCCAAAGCTAGTCAGGTAACTCAATAAATACCAAGATATTCCAGCA
 GATCGTAATCGCTTTGTGATCCCGATAATTGACAGGAACTGGAAAGCTAGCTAGCTGGGAGCTTGCAGCTC
 ACATGATAATAGTGAAGAGCAATTAGGCTTACCCACAGTACTGTGTTACAGCAGGATCACAAAGATTTC
 10 AGAGATTACTTAGTACAGGCTATAAGAAAATCATGGTAATACAAGACCATACTTGCTCTAGGCCAGCAGGG
 GTATCAGGCCATTATGTGTTGGGCCCTCATGATAAAACTATTATGGAGACTCTGCCGAGCTCAGGGCTCA
 TTGCAATAATGATGATAACATGAGGAAATCTGGCTTTCAGGTGTGCTATCTGTAATGGTATTAAACG
 TGTTATTTGACAGTATACAGTATATGCTTTACAGATCATTACACGGAAATACATACGCCATGCTTATT
 AACTTTTACGTGTAGATAAACATAACCTAATGCCCTG

15 1.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0269-1 / Schmitz 2/14 (serotype 1); SEQ ID NO: 134
 GATGATAGGCCCTCAGGAGAACGAGGAGTAATCTACGAGCATAGTTACCAAAACAGAACAAATTCC
 20 AAAGAGCAAAGGCAACTTATGCTGAGTAACTTACCTCTAGTCACAAAAGCAGAACTGACAGAGCTTGC
 TACCGCTCTGACAAAACACTGCTGNAATCAACCTAAAGAGCAGCAAGATAATGAAACAAAAGCTTTA
 ACCTCTGCAACAAAATTTACACTTAATACTCTGCAAGTACTGTGAGGAGACCTTATAGCCCAAGGCCAAC
 ATCAAAAGAGGTTAACAGCTGACTGAAACAGAGCTCATATGCTCAAGCAGATCACATTCAAAGAGACTGC
 ATTGTCAGAAACAAAAGCTGATCTCAGGAAACTACTCTGACTGAGTTAGTGGAAACAGTCAAACG
 25 TCTGCAACAAAATTTGCTAAGCTCATGCTATGATTAGCAACTCTGATGCTTACATAAAACGACTTAAACGG
 CTAAATGATAATACAAAAGCTTAAAGCTCAAGATTGGAGAACGCTTAAAGCTGACTTAGAAAATCAAAAGCTAA
 AGTAAAAGCATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAGAGCAGAACTTAGT
 CGCTTAAATCTGGCTCTGCTACTCAGAAGTACGATTGTGGGATAATACCATGAAAGCAGGCCAGGG
 30 ATCTCTGAAAGACTTAAAGAGGACTGTGTTATGGGATCAGCTTACATAATTTACAA
 AGAGCATGAGCAGATAAAATTGCCAAGCTAGTCCAGGTAACTCAATAATACCAAGATATTCCAGCA
 GATGCTAATCGCTTTGTGATCCCGATAATTGACACCAAGCTGCAAATGAGCTTACGGCAGTTGCAGCTC
 ACATGATTAATAGTGTAAAGAGCAATTAGGCTTACCCAGTACTGTGTTACAGCAGGATCACAAAGATTTC
 35 AAGATTACTTAGTACCGCTATAAGAAAATCATGGTAATACAAGACCATACTTGCTCTAGGCCAGCAGGG
 GTATCAGGCCATTATGTGTTGGGCCCTCATGATAAAACTATTATGGAGACTCTGCCGAGCTCAGGGCTCA
 TTGCAATAATGATGATAACATGAGGAAATCTGGCTTTCAGGTGTGCTATCTGTAATGGTATTAAACG
 TGTTATTTGACAGTATACAGTATATGCTTTACAGATCATTACACGGAAATACATACGCCATGCTTATT
 AACTTTTACGTGTAGATAAACATAACCTAATGCCCTG

> Spy0269-1 / Schmitz 1/156 (serotype 4); SEQ ID NO: 135
 GATGATAGGCCCTCAGGAGAACGAGGAGTAATCTACGAGCATAGTTACCAAAACAGAACAAATTCC
 40 AAAGAGCAAAGGCAACTTATGCTGAGTAACTTACCTCTAGTCACAAAAGCAGAACTGACAGAGCTTGC
 TACCGCTCTGACAAAATTTACACTTAATACTCTGCAAGTACTGTGAGGAGACCTTATAGCCCAAGGCCAAC
 ATCAAAAGAGGTTAACAGCTACTGAAACAGCTCTATACTGCTCAAGCAGATCACATTCAAAGAGACTGC
 ATTGTCAGAAACAAAAGCTGATCTCAGGAGAACACTCTGAGCAACTCTGAGCTTACAGGTTAGTGGAAACAGTCAAACGG
 45 TCTGCAACAAAATTTGCTAAGCTCATGTTATGCAAGTACTCTGATGCTATCTACTAAGCAGCTAAACCG
 CTAATGATAATACAAAAGCTTAAAGCTCAGAATTGGAGAGGCTTAAAGCTGACTTAGAAAATCAAAAGCTAA
 AGTAAAAGCATTGCTGAGGAGCTCAGGAGCTCAGAAAAGCTGCTTACAGCAGAAAAGAGCAGAACTTAGT
 CGCTTAAATCTGGCTCTGCTACTCAGAAGTACGATTGTGGTAAATACCATGAAAGCAGGCCAGGG
 50 ATCTCTGTAAGAAGCTTAAAGAGGACTGTGTTATGGGATCAGCTTACATAATTTACAA
 AGAGCATGAGCAGATAAAATTGAGGACTGTGTTATGGGATCAGCTTACATAATTTACAA
 GATGCTAATGCCCTGTTGATCCCGATAATTGACACAGAGCTCAGAAATGAGCTAGGCCAGTTGCAGCTC
 ACATGATTAATAGTGTAAAGAGCAATTAGGCTTACCCACAGTACTGTCAAGCAGGATCACAAAGAATTTC
 55 AAGATTACTTAGTACCGCTATAAGAAAATCATGGTAATACAAGACCATACTTGCTACGGAGCTCAGGGCTCA
 GTATCAGGCCATTATGTGTTGGGCCCTCATGATAAAACTATTATGGAGACTCTGCCGAGGGTCAAGGGCTCA
 TTGCAAAATGATGATAACATGAGGAAATCTGGCTTTACAGGTGTGCTACTGTGAAATGGTATTAAACG
 TGTTATTTGACAGTATACAGTATATGCTTTACAGATCATTACACGGAAATACATACGCCATGCTTATT
 AACTTTTACGTGTAGATAAACATAACCTAATGCCCTG

> Spy0269-1 / Schmitz 1/59 (serotype 12); SEQ ID NO: 136

60 GATGATAGGCCCTCAGGAGAACGAGGAGTAATCTACGAGCATAGTTACCAAAACAGAACAAATTCC

AAGAGGCCAAGGCAACTATTGATGCAGTTAAAGAAAACCTCAGTCACAAAAAGCAGAACGTGACAAAAGCTTGC
 TACCGCTCTGACAAAACACTCTGCTGAACCACTTAAAGGAGCAGCAAGATAATGACAAAAGCTTAA
 ACCTCTGCAAGAAAATTCTACATAACTCTGCAAGTAGTGGAGGACCTTATTGCCCAGGAGGCCAAC
 ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCTATACTGTCAGCAGATCAACATTCAAAGAGACTGC
 5 ATTGTCAGAACAAAAGCTAGCATTCAGCAGAACACTCTGAGCTCAAGATTAGTGAACACTTCAAAAGC
 TCTGACAAAGAAAATTCTGCTAACGCTCAAGTATTGATCTGATCTACTAAAGCAGCTCAACCG
 CTAAAGATAATCAAAGGATTAAAGCTCAGAATGGAGAGCTTAAAGCTGACTTAAAGGAGCTTAA
 AGTAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTCTAGCAGAAAAGGCCAACACTTGT
 10 CGTCTTAATCTCAGCTCCGTACTCAAGATAGCATTTGGGTTAATAATACCAGTAAAGCACCGCAAGGCT
 ATCCTCTGAGAACAGGACTTAAAAGTAGAGCTACTGGTTATTGGATACGCTAGTTACAAATAATTACAA
 AGAGCATGAGCATCAAATTATTGCTAACGAGCTTACCCAGTACTGTTACAGCAGGATCACAGAAATTG
 15 AAGATTACTTAGTACAGCTATAAAAACACTCTGAAATACGTTACAGGATCATTGCTCAGGCCAGGG
 GTATCAGGGCATTATGGTGTGGCCTCATGATAAAAACTTATTGAGACTCTGCCGAGGCTCAGGGCTCA
 TTGCAATGATGATAACATGAGGAAATCTGGCTGCTTTAACGATGTGCATACTGTAATGGTATTAAACG
 TGGTATTATTGAGCAGTATCAAGTATATGCTTTACAGATCATTTACCGGAAATACATACGCCATGCTATT
 AACTTTTACGTGTAGATAACGTAACCCATGCGCTGTT

20 > Spy0269-1 / Schmitz 1/177 (serotype 22); SEQ ID NO: 137
 GATGATAGGCCCTCAGGAGAACGAGGAGCTAACACTCAGCAGATGTTACCAAACAGAACAAATTCC
 AAGAGGCCAAGGCAACTATTGAGCAGTTGAAAAGGCTCTCAGTCACAAAAGCAGAACACTGACAGCTTGC
 TACCGCTCTGACAAAACACTCTGCTAAATCAACCCATTAAAGGAGCAGCAAGATAATGACAAAAGCTTAA
 ACCTCTGCAAGAAAATTCTACATAACTCTGCTAACGAGCTACTGTTACGAGGACCTTATTGCCAAGGCCAAC
 25 ATCAAAGAGAGTTAACAGCTACTGAAACAGCTTCTATACTGTCAGCAGATCAACATTCAAAGAGACTGC
 ATTGTCAGAACAAAAGCTAGCATTCAGCAGAAAACACTCTGAGCTCAAGATTAGTGTGACAAAGCTTAAAGC
 TCTGCAAGAAAATTCTGCTAACGCTATGTTAGTATCTGCTATCAGTAAAGCAGCTTACAGCAGCTAACCG
 30 TCTGAAATGATAACAAAAGCTTAAAGGAGCTTACAGGATCAGGAGCTTACAGGAGCTTACAGGAGCTAACAG
 AGTTAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAGAGGCCAACACTTGT
 CGTCTTAACTGCTCCGTACTCAAGATAGCATTTGGGTTAATAACCATGAAAGCAGCTTACAGGAGCTAACAG
 ATCTCTTGAAGAACCTTAAATTAGAGCTAGTTATTGGATCAGCTTACAGTAACTTACATATTACAA
 AGAGCATGAGCATCAAATTATTGCCAAGCTAGTCAGGTTAATACTAACATACCAAGATAATTCCAGCA
 35 GATGATCTAACGCTTGGTGTGGCCTATGGACACCCAGAGTGCAAAATGAGCTAGCGCAGTTGAGCTC
 ACATGATAATTAGTGAAGAACATTAGCTTACACCAGTACTGTCACACAGGATCACAGAAATTGTC
 AGGTTACTTAGTACAGCTATAAGGAAACCTCATGGTAAACAGACCATTATTGCTCTAGGCCAGGG
 GTATCAGGGCATTATGGTGTGGCCTCATGATAAAAACTTATTGAGACTCTGCCGAGGCTCAGGGCTCA
 TTGCAATGATGATAACATGAGGAAATCTGGTGTGGCTTAAAGCATGTGCATACTGTAATGGTATTAAACG
 TGGTATTATTGAGCAGTATCAAGTATATGCTTTACAGATCATTTACCGGAAATACATATGCCATGCTATT
 AACTTTTACGTGTAGATAACGTAACCCATGCGCTGTT

40 > Spy0269-1 / Schmitz 1/43 (serotype 22); SEQ ID NO: 138
 GATGATAGGCCCTCAGGAGAACGAGGAGCTAACACTCAGCAGATGTTACCAAACAGAACAAATTCC
 AAGAGGCCAAGGCAACTATTGAGCAGTTGAAAAGGCTCTCAGTCACAAAAGCAGAACACTGACAGCTTGC
 TACCGCTCTGACAAAATTCTACATAACTCTGCTAACGAGCTTATTGCTAACGAGATAATGACAAAAGCTTAA
 ACCTCTGCAAGAAAATTCTACATAACTCTGCTAACGAGCTTATTGCTAACGAGATAACATTCAAAGAGACTGC
 45 ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCTATACTGTCAGCAGATCAACATTCAAAGAGACTGC
 ATTGTCAGAACAAAAGCTGCTTCTGGAGAACACTCTGGAGCTAACGAGTAAAGTTAGTGGAAACAGTCAAAACG
 TCTGCAAGAAAATTCTGCTAACGCTATGTTAGTATCTGCTATCAGTAAAGCAGCTAACCG
 CTAACTGATAATCAAAGCATTAAGCTCAGAATTGGAGAGGCTAACGCTACTGACTTACAGGAAATTCAAAGCTAA
 AGTTAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTTACAGGAGAAAAGAGGCCAACACTTGT
 CGTCTTAACTCTCAGCTCCGTACTCAAGATAGCATTTGGGTTAATAACCATGAAAGCAGGCCAACGGT
 50 ATCTCTTGAAGAACCTTAAAGGAGCTAGTGGTTATTGGATCAGCTAGTTACAAATTATACAA
 AGAGCATGAGCATCAAATTATTGCCAAGCTAGTGGAGCTTACATTAATACATACCAAGATAATTCCAGCA
 GATGATCTAACGCTTGGTGTGGCCTATGGACACCCAGAGTGCAAAATGAGCTAGCGCAGTTGAGCTC
 ACATGATAATTAGTGAAGAACCTTAAAGGAGCTTACCCAGTACTGCTACTGAGCTAACAGGAGCTAACAG
 55 AGGTTACTTAGTACAGCTATAAGGAAACCTCATGGTAAACAGACCATTATTGCTCTAGGCCAGGG
 GTATCAGGGCATTATGGTGTGGCCTCATGATAAAAACTTATTGAGACTCTGCCGAGGCTCAGGGCTCA
 TTGCAATGATGATAACATGAGGAAATCTGGTGTGGCTTAAAGCATGTGCATACTGTAATGGTATTAAACG
 TGGTATTATTGAGCAGTATCAAGTATATGCTTTACAGATCATTTACCGGAAATACATATGCCATGCTATT
 AACTTTTACGTGTAGATAACGTAACCCATGCGCTGTT

> Spy0269-1 / Schmitz 1/136 (serotype 25); SEQ ID NO: 139
 GATGATAGGCCCTCAGGAAACGAAGGGAGTAATCTCACGACGATAGTTACCAAAACCAGAAAACAATT
 CAAAGGAGCCAAGGCAACTATTGTGAGCTGTGAAACAAAACCTCTCAGTCACAAAAAGCAGAACTGCAGAGCTTGC
 5 TACCGCTCTGACAAAACACTACTGCTGAATCAACCACTTAAAGGAGCAGCAAGATAATGACAAAAGGCTTAA
 ACCTCTGACAAAGAAATTACTACTCTGCAAGTACTCTGCAAGTAGTGGAGAGCCATTAGGCCAAGGAGCCGAAC
 ATCAAGAGAGTAAACGACTGAAACAGAGCTTACAGCTCATGATGATTAGCAATCTGATCTACTAAAGCAGCTTAA
 10 ATTGTCAGAAACAAAAGCTAGCATTTGCAAGGAGCTTAAAGCTGACATTTAGGAAACAGACTGC
 ATTCAGAAACAAAAGCTAGCATTTGCAAGGAGCTTAAAGCTGACATTTAGGAAACAGACTGC
 15 ATCCCTTGAAGAACCTTAAAGGAGCTTAAAGCTGAGCTTAAAGGAGCTTAAAGCTGACATTAGAAACATTCAGCA
 AGAGCATGAGCATCAAATTATTGCCAAAGCTAGCTCAGGATTAACTAAATACAACTAACAGAATTTCAGCA
 GATCGTAATCGCTTGTGATCCCGATAATTGACACCAAGAGTGCAAAATGAGCTAGCCAGTTGCAGCTC
 20 ACATGATTAATAGTGTAAAGAACATACTGGCTTACAGGAGCTTAAAGCTGCTTAACTGGATGCAACTGTGAA
 AGGTTACTTAGCAGCTATAAAACATCTGAGGAGCTTAAAGCTGCTTAACTGGATGCAACTGTGAA
 TTGCAAGGCGATTATGGTTGGGCCATGATAAAACATTATGGAAAGACTCTGCCGAGCGCTCAGGGCTCA
 TTGCAAGATGATGATAACATGAGGAGATACTCGGTCTTAACTGGATGCAACTGTGAA
 25 TGTTATTATGAGCAGTCAAGTATGCTCTTACAGATCATTACAGGAAATACATGCCGATGCTTAA
 AACTTTTACGTGTAGATAAACGTAACCTAATGCCGCTT
 > Spy0269-1 / Schmitz 1/85 (serotype 28); SEQ ID NO: 140
 GATGATAGGCCCTCAGGAAACGAAGGGAGTAATCTCACGACGATAGTTACCAAAACCAGAAAACAATT
 25 AAAGGAGCCAAGGCAACTATTGTGCACTGAAAAAAACTCTCAGTCACAAAAAAAGCAGAACTGCAGAGCTTGC
 TACCGCTCTGACAAAACACTACTGCTGAATCAACCACTTAAAGGAGCAGCAAGATAATGACAAAAGGCTTAA
 ACCTCTGACAAAGAAATTACACTACTCTGCAAGTAGTGGAGAGCCATTAGCCCAGGCGCAAGAC
 ATCAAAAGAGTAAACGACTGAAACAGGCTTACATAAGCTCAGCAGATCAACATTCAAAGAGACTGC
 30 ATGTGAGACAAAAGCTAGCATTCAGCAGAAACTACTCGAGCTCAAGATTAGGAAACAGCTTAAAGCAGCTTAA
 TCTGAAACAAAATTCGCTAAGCTGATGAGCTTACAGGAGCTTAAAGCTGCTTAACTGGATGCAACTGTGAA
 35 ATGATGATAATACAAAGGCTAAAGGAGCTTAAAGGAGCTTAAAGCTGACTTAAAGGAGCTTAAAGCTGAA
 AGTAAAGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGCTGACTTAAAGGAGCTTAAAGGAGCTTAA
 ATCTCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 40 ATGATGATAATACAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 AGAGCATGAGCATCAAATTATTGCCAAAGCTGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 GATGATAATACAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 GTATCAGGGCATTATGGTTGGGCCCTCATGATAAAACATTATGGAGACTCTGCCGAGGCTCAGGGCTCA
 TTGCAAGATGATAACATGAGGAGATACTCGGTCTTAACTGGATGCAACTGTGAA
 45 TGTTATTATGAGCAGTATCAAGTATGCTCTTACAGATCATTACAGGAAATACATGCCGATGCTTAA
 AACTTTTACGTGTAGATAAACATAACCTAATGCCGCTT
 > Spy0269-1 / Schmitz 1/85 (serotype 28); SEQ ID NO: 141
 GATGATAGGCCCTCAGGAAACGAAGGGAGTAATCTCACGACGATAGTTACCAAAACCAGAAAACAATT
 50 AAAGGAGCCAAGGCAACTATTGTGCACTGAAAAAAACTCTCAGTCACAAAAAGCAGAACTGCAGAGCTTGC
 TACCGCTCTGACAAAACACTCTGCAATCAACCCACTTAAAGGAGCAGCAAGATAATGACAAAAGGCTTAA
 ACCTCTGACAAAGAAATTACACTACTCTGCAAGTAGTGGAGAGCCATTAGCCCAGGAGGCCGAAC
 ATCAAAAGAGTAAACGACTGAAACAGAGCTTACATAAGCTCAGTAGATCAACATTCAAAGAGACTGC
 55 ATTGTGAGACAAAAGCTAGCATTCAGCAGAAACTACTCGAGCTCAAGATTAGGAAACAGCTTAAAGGAGCTTAA
 TCTGAAACAAAATATTGCTAAGCTCATGATGATTACAGTACTCTGATGCTTACATAAGGAGCTTAAAGGAGCTTAA
 CTGATGATAATACAAAGGCTAAAGCTGAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 60 AGTAAAGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 AGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 AGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 GTATCAGGGCATTATGGTTGGGCCCTCATGATAAAACATTATGGAGACTCTGCCGAGGCTCAGGGCTCA

> Spy0269-1 / Schmitz 1/85 (serotype 28); SEQ ID NO: 142
 GATGATAGGCCCTCAGGAAACGAAGGGAGTAATCTCACGACGATAGTTACCAAAACCAGAAAACAATT
 65 AAAGGAGCCAAGGCAACTATTGTGCACTGAAAAAAACTCTCAGTCACAAAAAGCAGAACTGCAGAGCTTGC
 TACCGCTCTGACAAAACACTCTGCAATCAACCCACTTAAAGGAGCAGCAAGATAATGACAAAAGGCTTAA
 ACCTCTGACAAAGAAATTACACTACTCTGCAAGTAGTGGAGAGCCATTAGCCCAGGAGGCCGAAC
 ATCAAAAGAGTAAACGACTGAAACAGAGCTTACATAAGCTCAGTAGATCAACATTCAAAGAGACTGC
 70 ATTGTGAGACAAAAGCTAGCATTCAGCAGAAACTACTCGAGCTCAAGATTAGGAAACAGCTTAAAGGAGCTTAA
 TCTGAAACAAAATATTGCTAAGCTCATGATGATTACAGTACTCTGATGCTTACATAAGGAGCTTAAAGGAGCTTAA
 CTGATGATAATACAAAGGCTAAAGCTGAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 75 AGTAAAGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 AGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 AGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 80 AGTATGATAATACAGTGTAAAGAAGCAATTAGGCTTACCCAGCTTACAGTGTGAA
 AAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 AGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAA
 GTATCAGGGCATTATGGTTGGGCCCTCATGATAAAACATTATGGAGACTCTGCCGAGGCTCAGGGCTCA

TTCGAATGATAACATGTACGGAAATATCGGTCTTTAACGATGTCAACTGTGAATGGTATTAAACG
TGGTATTATGACAGTAACTAGTATGCTCTTACAGATCATTTACCGGAAATACATACGGCCATGCTATT
AACTTTACGTTAGATAAACGTAACCCATAAGCGCTGT

- 5 > Spy0269-1 / Schmitz 1/123 (serotype 49); SEQ ID NO: 142
GATGATAGGCCCTCAGGAGAACGAGGGAGTAACACTCACGACGATAGTTACCAAAACCAGAAAACATT
AAGAGCCAAGGCAACTATTGAGCAGTTGAAAAAAACTCTCAGTCACAAAAGCAGAAGCTGCAGAGCTTGC
TACCGCTCTGACAAAACACTACTGCTGAAATCAACCTTAAAGAGCAGCAAGATAATGAAACAAAAGCTT
ACCTCTGACAAGAAATTACACTAAACTACTCTTGCAAGTAGTGTAGGGAGACGCTTATTAGCCCAAGGAGCCGAA
10 ATCAAAGAGAGTTAACGCTACTGAAACAGAGCTTACATGCTCAAGCAGATCAACATTCAAAAGGAGACTGC
ATTGTCAGAACAAAAGCTAGATTCTACGAGAAAACACTACTGCTGACGCTCAAGATTAGTGGACAACTGAA
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCTGTATCAACTAAAGCAGCTTAAACCG
CTAATGATAATACAAAGCATTAAGCTCAAGTATTGGAGAAGCTTAAAGCTGACTTAAAGATC
AGTAAAGAACGTAATGACTGAAAGACTGTTGGAGAAGCTTAAAGCTGACTTAAAGATC
15 CGCTTAAATCCTCAGCTCGCTACTCAAGATGATTCTGGGTTAATAACATGAAAGCAGCCAGGG
ATCCCTGAGAACAACTTAAAATAGAGCTAGTGGTTATTGGATCAGCTAGTACATAATTATTACAA
AGAGCATGAGCATCAAATTATTGCAAAAGCTAGTCCAGGTAACTCAATAACATACCAAGATTC
GAGCATGAGCATCAAATTATTGCAAAAGCTAGTCCAGGTAACTCAATAACATACCAAGATTC
20 AGATGAGCATGAGCATCAAATTATTGCAAAAGCTAGTCCAGGTAACTCAATAACATACCAAGATTC
AAGATTACTTAGTACAGGCTATAAGAAAACATGGTAAACAGACCATCATTGTCAG
GTATCAGGGCATATTGCTGTGGCCCTCATGAAAAAACTTATTAGAAGACTCTGCCGAGCTGAGGCTCA
TTCGAATGATAACATGAGGAAATATCGGTCTTTAACGATGTGCAACTGTGAATGGTATTAAACG
TGGTATTATGACAGTATCAAGTATATGCTCTTACAGATCATTTACCGGAAATACATATGGCATGCTATT
AACTTTACGTTAGATAAACGTAACCCATAAGCGCTGT
- 25 > Spy0269-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 143
GATGATAGGCCCTCAGGAGAACGAGGGAGTAACACTCACGACGATAGTTACCAAAACCAGAAAACATT
AAGAGCCAAGGCAACTATTGAGCAGTTGAAAAAAACTCTCAGTCACAAAAGCAGAAGCTGCAGAGCTTGC
TACCGCTCTGACAAAACACTACTGCTGAAATCAACCACTTAAAGAGCAGCAAGATAACGAAACAAAAGCTT
30 ACCTCTGACAAGAAATTACACTCTGCAAGTAGTCTGGCAAGTAGTGTAGGGAGACGCTTATTAGCCCAAGGAGCCGAA
ATCAAAGAGAGTTAACGACTGAAACAGCTTCAATACTGCTCAAGCAGATCAACATTCAAAGAGACTGC
ATTGTCAGAACAAAAGCTAGATTTCAGCAGAGAAAACACTACTGCAAGCTCAAGATTAGTGGAAAGCTAAAGC
TCTGAACAAAATATTGCTAAGCTGACTGTATGATTAGCAACCTGTGCTACTAAAGCAGCTCAAACCG
CTAATGATAATACAAAGCATTAAGCTCAGAATTGGAGAAGCTTAAAGCTGACTTAAAGATC
35 AGTTAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTCTGCTAGCAGAAAAGAGCAGAACTT
CGCTTAAATCCCTCAGCTCGCTACTCAAGATGATTCTGGGTTAATAACCATGAAAGCAGCCAGGG
ATCCCTGAGAACCTTAAAATAGAAGCTAGTGGTTATTGGATCAGCTAGTTACATAATTATTACAA
AGAGCATGAGCATCAAATTATTGCAAAAGCTAGTCCAGGTAACTCAATAACATACCAAGATATTCCAGCA
40 GactgtatcgtttGTGATGCCGATAATTGACACAGGAGTGCAGGAAATGAGCTAGCCGAGTTGCGACT
ACATGATTAATAGTGTAAAGAGACAATTAGGTCTACCCAGTTACTGTCTCAGCAGGAGTCAGAAATTG
AAGATTACTTAGTACAGCTATAAGAAAACACTGTGAAATACACGACCATATTGGCTACTAGGAGCAGGG
GTATCAGGGCATATTGCTGTGGCCCTCATGATAAAAACATTATTAGAAGACTCTGCCGAGCTCAGGGCTCA
TTCGAATGATGATAACATGAGGAAATATCGGTCTTTAACGATGTGCAACTGTGAATGGTATTAAACG
TGGTATTATGACAGTATCAAGTATATGCTCTTACAGATCATTTACCGGAAATACATATGGCATGCTATT
45 AACTTTACGTTAGATAAACGTAACCCATAAGCGCTGT

2. Spy0292

2.1 Full length Spy0292

- 50 > Spy0292 / SF370 (serotype 1); SEQ ID NO: 144
ATGATCAAACGATTAATTCCCTAGTGTCTCATGCCCTTATTGGCAGCAAGCACTGTGTTAGCCGTGAAGAGT
ATTGCTTAAGCTGTAAGCATGCGATTGCCGTGACCTTGAAGTGGCAAGATTTTATACGAAAAGATGCTAA
AGAAGTTGTCCTCAGTCGCTCAGTCAGTAAGCTCTTGACACCTATCTGGTTTACAAGAAGTTCTAAGGG
55 AACGCTAAATGGGATATTGCTCTGAACTACTTCTAACCTTATGACACTACAAACACTACTAATATTAGTA
ACGTTCTCTTGTAAAGAAAATACCGTTAAAGAACCTTAAAGCTGCTTAGTGTAAATACGCCAATAG
CCCCGCTATTGCTTAGCTAAAAAATAGCGGAAACGCAACCCAAATTGGACAAAGTAAAGACAA
AGACGAAATGGGATATTGCTGAAAGCTGCTAACCTTACGCTTAACTAACCAATTGGGTTAGGAGCTAATA
CTTATCCTAATACAGAACAGATGATAAAATTGTTGGCCCTACTGATTAGCTATTATGCCCAGGCTAT
60 CTTATTAGAATTTCAGAAGTACTGAAATTCTAGCAACCTCTACTATTGGACAAACCCATTAC

AGTTATAATTACATGCTTAAAGGCATGCCCTGTTATCGAGAAGGGGTGGATGGCTTTTGTTGGTTATCTA
 AAAAGCCGGTCTTCTTGTAGCTACTAGTGTGAAAATCAAAATGAGGGTTATTACAGTAGTTTAAATGC
 TGATCAAAGGCCAGGAGTATTAGCTATTTAAACACCAACATCAATTGTTGAGTCACCTTTAAAT
 TTTCAAAAGTCAGTTAATGAAAAATAAACCAGTAAAGGGTATATGCTTAGACAGTCTAAAAAA
 5 CTGTCAAACTGTAGCCAAAATAGTTTATTCACCAACATACACAAGAACAAAATACCGTCCA
 TATTACTAAAGAAATCATCCACATGATGCCACCTCTACAAAGGGACAAGCTTAGGTAGAGCACCCCTCAA
 GATAAACATCTTATTGAGAAGGGTATCTGGACTCTCTTCTATCAACTTATCTTCAAAACATT
 CTAAAGTTCTTTAAAGGCTGGGAACCGTTGTGAGGTATGTCATAACCTCTTATAG

10 2.2 Antigenic fragment Spy0292-1

> Spy0292-1 / SF370 (serotype 1); SEQ ID NO: 12
 GAAGACTATTGGTAACTCTGAACATGGATTGGCGTGGACCTTGAAGGTGCAAAGTTTATACGAAAAG
 ATGCTAAAGAAGTGTCCAGTCGGCTCAGTCAGTCACTAGCTGCTTACACCTATCTGGTTACAAAGAAGTTTC
 15 TAAGGGCAAGCTAAATGGGATAGTCTGTAACTATTCTAACTACCCATTGAACTACTACAAACTATAC
 ATTAGTAACCTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTAAAGTGCCTAGTTAATACG
 CCAATAGCCCCCTATTGCTTTAGCTGAAAATAGGGCAAGCCGAAACCCAAATTGTTGACAAAATGAAAAA
 ACAATTAAAGACAATGGGATTTCCGATGCAAAAGGTGCTCAATTCAACTGGCTTAACTAACCATTAGGA
 20 GCTAATACTATCTAAACAGAACCGAGTGTGAAAATTGTTTTGC

20 2.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0292-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 145
 GAAGACTATTGGTAACTCTGAACATGGATTGGCGTGGACCTTGAAGGTGCAAAGTTTATACGAAAAG
 25 ATGCTAAAGAAGTGTCCAGTCGGCTCAGTCAGTCACTAGCTGCTTACACCTATCTGGTTACAAAGAAGTTTC
 TAAGGGCAAGCTAAATGGGATAGTCTGTAACTATTCTAACTACCCATTGAACTACTACAAACTATAC
 ATTAGTAACCTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTAAAGTGCCTAGTTAATACG
 CCAATAGCCCCCTATTGCTTTAGCTGAAAATAGGGCAAGCCGAAACCCAAATTGTTGACAAAATGAAAAA
 ACAATTAAAGACAATGGGATTTCCGATCAAAAGGTGCTCAATTCAACTGGCTTAACTAACCATTAGGA
 30 GCTAATACTATCTAAACAGAACCGAGTGTGAAAATTGTTTTGC

> Spy0292-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 146
 GAAGACTATTGGTAACTCTGAACATGGATTGGCGTGGACCTTGAAGGTGCAAAGTTTATACGAAAAG
 ATGCTAAAGAAGTGTCCAGTCGGCTCAGTCAGTCACTAGCTGCTTACACCTATCTGGTTACAAAGAAGTTTC
 35 TAAGGGCAAGCTAAATGGGATAGTCTGTAACTATTCTAACTACCCATTGAACTACTACAAACTATAC
 ATTAGTAACCTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTAAAGTGCCTAGTTAATACG
 CCAATAGCCCCCTATTGCTTTAGCTGAAAATAGGGCAAGCCGAAACCCAAATTGTTGACAAAATGAAAAA
 ACAATTAAAGACAATGGGATTTCCGATCAAAAGGTGCTCAATTCAACTGGCTTAACTAACCATTAGGA
 GCTAATACTATCTAAACAGAACCGAGTGTGAAAATTGTTTTGC

> Spy0292-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 147
 GAAGACTATTGGTAACTCTGAACATGGATTGGCGTGGACCTTGAAGGTGCAAAGTTTATACGAAAAG
 ATACTAAAGAAGTGTCCAGTCGGCTCAGTCAGTCACTAGCTTGAACACCTATCTGGTTACAAAGAAGTTTC
 TAAGGGCAAGCTAAATGGGATAGTCTGTAACTATTCTAACTACCCATTGAACTACTACAAACTATAC
 45 ATTAGTAACCTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTAAAGTGCCTAGTTAATACG
 CCAATAGCCCCCTATTGCTTTAGCTGAAAATAGGGCAAGCCGAAACCCAAATTGTTGACAAAATGAAAAA
 ACAATTAAAGACAATGGGATTTCCGATGCAAAAGGTGCTTAACTCAACTGGCTTAACTAACCATTAGGA
 GCTAATACTATCTAAACAGAACCGAGTGTGAAAATTGTTTTGC

50 > Spy0292-1 / Schmitz 1/74 (serotype 3); SEQ ID NO: 148

GAAGACTATTGGTAACTCTGAACATGGATTGGCGTGGACCTTGAAGGTGCAAAGTTTATACGAAAAG
 ATGCTAAAGAAGTGTCCAGTCGGCTCAGTCAGTCACTAGCTTGAACACCTATCTGGTTACAAAGAAGTTTC
 TAAGGGCAAGCTAAATGGGATAGTCTGTAACTATTCTAACTACCCATTGAACTACTACAAACTATAC
 ATTAGTAACCTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTAAAGTGCCTAGTTAATACG
 55 CCAATAGCCCCCTATTGCTTTAGCTGAAAATAGGGCAAGCCGAAACCCAAATTGTTGACAAAATGAAAAA
 ACAATTAAAGACAATGGGATTTCCGATGCAAAAGGTGCTTAACTCAACTGGCTTAACTAACCATTAGGA
 GCTAATACTATCTAAACAGAACCGAGTGTGAAAATTGTTTTGC

60 > Spy0292-1 / Schmitz 1/76 (serotype 22); SEQ ID NO: 149

GAAGACTATTGGTAACTCTGAACATGGATTGGCGTGGACCTTGAAGGTGCAAAGTTTATACGAAAAG

- ATGCTAAAGAAGTGTGCCCCGTGCCCTCAGTCAGTAAGCTTGAACACCTATCTGGTTTACAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGAACTATTCTAACCCTTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAAATACCGCTTAAAGAACCTTAAAGTCGTTAGTGTAAATAAG
CCAAATAGCCCCGCTATTGCTTAAAGCCTTAAAGGGGAACCGGAACCCAAATTGTTGACAAAATGAAAAA
5 5 ACAATTAAAGACAATGGGGCATTCGGATGCAAAGGTCGTAACTCACTGGCTTAACTAACCAATTTTTAGGA
GCTAATACTTATCTTAATACAGAACAGATGATGaaaATTGTTTTGC
- > Spy0292-1 / Schmitz 1/92 (serotype 11); SEQ ID NO: 150
10 GAAGAGTATTCGGAACCTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAG
ATGCTAAAGAAGTGTGCCCCGTGCCCTCAGTCAGTAAGCTTGAACACCTATCTGGTTTACAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTCTAACCCTTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAAATACCGCTTAAAGAACCTTAAAGTCGTTAGTGTAAATAAG
20 CCAATAGCCCCGCTATTGCTTAAAGCCTTAAAGGGGAACCGGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGACAATGGGGCATTCGGATGCAAAGGTCGTAACTCACTGGCTTAACTAACCAATTTTAGGA
GCTAATACTTATCTTAATACAGAACAGATGATGAAAATTGTTTTGC
- > Spy0292-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 151
25 GAAGAGTATTCGGAACCTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAG
ATGCTAAAGAAGTGTGCCCCGTGCCCTCAGTCAGTAAGCTTGAACACCTATCTGGTTTACAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTCTAACCCTTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAAATACCGCTTAAAGAACCTTAAAGTCGTTAGTGTAAATAAG
30 CCAATAGCCCCGCTATTGCTTAAAGCCTTAAAGGGGAACCGGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGACAATGGGGCATTCGGATGCAAAGGTCGTAACTCACTGGCTTAACTAACCAATTTTAGGA
GCTAATACTTATCTTAATACAGAACAGATGATGAAAATTGTTTTGC
- > Spy0292-1 / Schmitz 1/142 (serotype 83); SEQ ID NO: 152
35 GAAGAGTATTCGGAACCTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAG
ATGCTAAAGAAGTGTGCCCCGTGCCCTCAGTCAGTAAGCTTGAACACCTATCTGGTTTACAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTCTAACCCTTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAAATACCGCTTAAAGAACCTTAAAGTCGTTAGTGTAAATAAG
40 CCAATAGCCCCGCTATTGCTTAAAGCCTTAAAGGGGAACCGGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGACAATGGGGCATTCGGATGCAAAGGTCGTAACTCACTGGCTTAACTAACCAATTTTAGGA
GCTAATACTTATCTTAATACAGAACAGATGATGAAAATTGTTTTGC
- > Spy0292-1 / Schmitz 1/144 (serotype 76); SEQ ID NO: 153
45 GAAGAGTATTCGGAACCTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAG
ATGCTAAAGAAGTGTGCCCCGTGCCCTCAGTCAGTAAGCTTGAACACCTATCTGGTTTACAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTCTAACCCTTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAAATACCGCTTAAAGAACCTTAAAGTCGTTAGTGTAAATAAG
50 CCAATAGCCCCGCTATTGCTTAAAGCCTTAAAGGGGAACCGGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGACAATGGGGCATTCGGATGCAAAGGTCGTAACTCACTGGCTTAACTAACCAATTTTAGGA
GCTAATACTTATCTTAATACAGAACAGATGATGAAAATTGTTTTGC
- > Spy0292-1 / Schmitz 1/194 (serotype 44); SEQ ID NO: 154
45 GAAGAGTATTCGGAACCTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAG
ATGCTAAAGAAGTGTGCCCCGTGCCCTCAGTCAGTAAGCTTGAACACCTATCTGGTTTACAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTCTAACCCTTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAAATACCGCTTAAAGAACCTTAAAGTCGTTAGTGTAAATAAG
50 CCAATAGCCCCGCTATTGCTTAAAGCCTTAAAGGGGAACCGGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGACAATGGGGCATTCGGATGCAAAGGTCGTAACTCACTGGCTTAACTAACCAATTTTAGGA
GCTAATACTTATCTTAATACAGAACAGATGATGAAAATTGTTTTGC
- 2.4 Antigenic fragment Spy0292-3**
- > Spy0292-3 / SF370 (serotype 1); SEQ ID NO: 13
55 GAAGAGTATTCGGAACCTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAG
ATGCTAAAGAAGTGTGCCCCGTGCCCTCAGTCAGTAAGCTTGAACACCTATCTGGTTTACAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTCTAACCCTTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAAATACCGCTTAAAGAACCTTAAAGTCGTTAGTGTAAATAAG
60 CCAATAGCCCCGCTATTGCTTAAAGCCTTAAAGGGGAACCGGAACCCAAATTGTTGACAAAATGAAAAA

5 ACAATTAAAGACAATGGGGATTTCGATGCAAAGGTGCTAATTCAACTTGCTTAACCTAACCATTTTTAGGA
 GCTAATACTTATCTCTAAATCAGAACAGATGATGAAAATGTTTCTGGCCACTGATTAGCTATTATTGCCA
 GGCATCTCTTATTAGAATTTCAGAACGACTGTAATTATCTAGCAAATCTCCACTATTGGCTGGACAAAC
 CATTGCAACTGTTAATTACATGCTTAAAGGCATGCCCTGTGTTATCGAGAAGGGTGGATGGCTTTTGGT
 10 TATTCTAAAAAGCCGGTCTCTTTGTAGCTACTGTGCTGAAATCAAAACACCAATCAATTGAGGGTTATTACAGTAGTT
 TAATGCTGATCAAAACGCCAGGGATGATTAGCTATTATAAAACACCAATCAATTGTCAGTACCTTT
 AATTAAATTCTCAAAAGTCAGTTAATTGAA

10 2.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

10 > Spy0292-3 / Schmitz 1/39 (serotype 12); SEQ ID NO: 155
 GAAGAGTATTGGTAACTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
 ATGCTAAAGAGTTGCTCCAGTCAGTCAAGCTTGAACCAACCTATCTGGTTACAAAGAAGTTTC
 15 TAAGGGCAAGCTAAATTGGGATAGTCTGTTAAGTCTTCAACTACCCCTATGAACTCACTAACAACTACT
 ATTAGTAACGTTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTTAAGTGGCTTACTGTTAATAAAG
 CCAATAGGCCGCTATTGCTTGTGCTGAAAAAATAGGCCGAACCCAAATTTGGTGAACAAATGGG
 20 ACAATTAAAGACATGGGGATTTCGATGCAAAGGTGCTAATTCAACTGCCCTTAACCTAACCATTTTAGGA
 GCTAATACTTATCTTAACAGAACGAGatGATGAAAATTGTTTGCCTGACTGATTAGCTATTATGGCA
 GGCATCTCTTATTAGAATTTCAGAACGACTGTAATTATCTAGCAAATCTCCACTATTGGTGAACAAAC
 CATTACAGTTAAATACATGCTTAAAGGCATGCCCTGTGTTATCGAGAAGGGTGGATGGCTCTTTGCGT
 25 TATTCTAAAAAGCCGGTCTCTTTGTAGCTACTGTGCTGAAATCAAAACACCAATCAATTGTCAGTACCTTT
 TAATGCTGATCAAAACGCCAGGGATGATTAGCTATTATAAAACACCAATCAATTGTCAGTACCTTT
 AATTAAATTCTCAAAAGTCAGTTAATTGAA

25 > Spy0292-3 / Schmitz 1/55 (serotype 118); SEQ ID NO: 156
 GAAGAGTATTGGTAACTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
 ATGCTAAAGAGTTGCTCCAGTCAGTCAAGCTTGAACCAACCTATCTGGTTACAAAGAAGTTTC
 30 TAAGGGCAAGCTAAATTGGGATAGTCTGTTAAGTCTTCAACTACCCCTATGAACTCACTAACAACTACT
 ATTAGTAACGTTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTTAAGTGGCTTACTGTTAATAAAG
 CCAATAGGCCGCTATTGCTTGTGCTGAAAAAATAGGCCGAACCCAAATTTGGTGAACAAATGGG
 35 ACAATTAAAGACATGGGGATTTCGATGCAAAGGTGCTAATTCAACTGCCCTTAACCTAACCATTTTAGGA
 GCTAATACTTATCTTAACAGAACGAGATGATGAAAATTGTTTGCCTGACTGATTAGCTATTATGGCA
 GGCATCTCTTATTAGAATTTCAGAACGACTGTAATTATCTAGCAAATCTCCACTATTGGTGAACAAAC
 CATTACAGTTAAATACATGCTTAAAGGCATGCCCTGTGTTATCGAGAAGGGTGGATGGCTCTTTGCGT
 40 TATTCTAAAAAGCCGGTCTCTTTGTAGCTACTGTGCTGAAATCAAAACACCAATCAATTGTCAGTACCTTT
 TAATGCTGATCAAAACGCCAGGGATGATTAGCTATTATAAAACACCAATCAATTGTCAGTACCTTT
 AATTAAATTCTCAAAAGTCAGTTAATTGAA

40 > Spy0292-3 / Schmitz 1/56 (serotype 28); SEQ ID NO: 157
 GAAGAGTATTGGTAACTGCTAAGCATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
 ATGCTAAAGAGTTGCTCCAGTCAGTCAAGCTTGAACCAACCTATCTGGTTACAAAGAAGTTTC
 45 TAAGGGCAAGCTAAATTGGGATAGTCTGTTAAGTCTTCAACTACCCCTATGAACTCACTAACAACTACT
 ATTAGTAACGTTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTTAAGTGGCTTACTGTTAATAAAG
 CCAATAGGCCGCTATTGCTTGTGCTGAAAAAATAGGCCGAACCCAAATTTGGTGAACAAATGGG
 50 ACAATTAAAGCCTATTGGGATTCGATGCAAAGGTGCTTAAATTCAGCTTAACCTAACCATTTTAGGA
 GCTAATACTTATCTTAACAGAACGAGATGATGAAAATTGTTTGCCTGACTGATTAGCTATTATGGCA
 GGCATCTCTTATTAGAATTTCAGAACGACTGTAATTATCTAGCAAATCTCCACTATTGGTGAACAAAC
 CATTACAGTTAAATACATGCTTAAAGGCATGCCCTGTGTTATCGAGAAGGGTGGATGGCTCTTTGCGT
 55 TATTCTAAAAAGCCGGTCTCTTTGTAGCTACTGTGCTGAAATCAAAACACCAATCAATTGTCAGTACCTTT
 TAATGCTGATCAAAACGCCAGGGATGATTAGCTATTATAAAACACCAATCAATTGTCAGTACCTTT
 AATTAAATTCTCAAAAGTCAGTTAATTGAA

55 > Spy0292-3 / Schmitz 1/74 (serotype 3); SEQ ID NO: 158
 GAAGAGTATTGGTAACTGCTAACATGGATTGCCGTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
 ATGCTAAAGAGTTGCTCCAGTCAGTCAAGCTTGAACCAACCTATCTGGTTACAAAGAAGTTTC
 60 TAAGGGCAAGCTAAATTGGGATAGTCTGTTAAGTCTTCAACTACCCCTATGAACTCACTAACAACTACT
 ATTAGTAACGTTCTCTGTATAAGAGAAAATACCGTTAAAGAACCTTTAAGTGGCTTACTGTTAATAAAG
 CCAATAGGCCGCTATTGCTGTTAGCTGCTGAAAAAATAGGCCGAACCCAAATTTGGTGAACAAATGGG
 ACAATTAAAGCCTATTGGGATTCGATGCAAAGGTGCTTAAATTCAGCTTAACCTAACCATTTTAGGA
 GCTAATACTTATCTTAACAGAACGAGATGATGAAAATTGTTTGCCTGACTGATTAGCTATTATGGCA

GGCATCTTATTAGAATTCCAGAAGTACTGAAATTATCTGACCAAATCTCCACTATTTTGCTGGACAACAC
CATTTCACTGGTAATTATCAGTCCTTAAAGGCATGCCCTGTATCGAGAAGCGTGGATGGCTTTGGT
TATTCTAAAAAGCCGGTCTCTTGTAGCTACTAGTCGAAAATCAAATGAGGGTTATTACAGTAGTT
TAAATGCTGATCAAGCCACGAGGATGATTAGCTATATTAAACAACCAATCAATTGTCAGTACCTTT
5 AATTATTTCAAAAGTCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/76 (serotype 22); SEQ ID NO: 159
GAAGAGTATTCTGGTAACTGCTAACGATGGATTGCCCTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
ATGCTAAAGAAGTGTCCCTGCGCTCAGTCAGTAAGCTCTTGACAAACCTATCTGGTTACAAAGAAGTTTC
10 TAAGGCGAACGTTAATTGGGATAGCTGTAACTATTCTAACTACCCCTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAATACCGTTAAAGAACTTTAAGTGGCTTAGTGTATAACG
CCAATAGCCCCGTTAGTCTTAGCTGAGAAAATAGGCGGAACCGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGACGTTAAGGCGATTAGCTGAACTACCCCTATGAACTCACTACAAACTATAC
15 GCTAATACCTATCTTAAAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGATGGACAAAC
GGCATCTTATTAGAATTCCAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGATGGACAAAC
CATTCTAACGTTAATTACATGCTTAAAGGCATGCCCTGTATCGAGAAGCGTGGATGGCTTTGGT
TATTCTAAAAAGCCGGTCTCTTGTAGCTACTAGTCGAAAATCAAATGAGGGTTATTACAGTAGTT
TAAATGCTGATCAAGCCACGAGGATGATTAGCTATATTAAACAACCAATCAATTGTCAGTACCTTT
AATTATTTCAAAAGTCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/92 (serotype 11); SEQ ID NO: 160
GAAGAGTATTCTGGTAACTGCTAACGATGGATTGCCCTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
ATGCTAAAGAAGTGTCCCTGCGCTCAGTCAGTAAGCTCTTGACAAACCTATCTGGTTACAAAGAAGTTTC
TAAGGCGAACGTTAATTGGGATAGCTGTAACTATTCTAACTACCCCTATGAACTCACTACAAACTATAC
25 ATTAGTAACGTTCTCTTGTATAAGAAAATACCGTTAAAGAACTTTAAGTGGCTTAGTGTATAACG
CCAATAGCCCCGTTAGTCTTAGCTGAGAAAATAGGCGGAACCGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGGCAATTGGGCAATTCCGATGCAAAGGCTGCTAACTCAACTACCAATTTTTGTAG
GCTAATACCTATCTTAAAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGATGGACAAAC
GGCATCTTATTAGAATTCCAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGCTGGACAAAC
30 CATTCTAACGTTAATTACATGCTTAAAGGCATGCCCTGTATCGAGAAGCGTGGATGGCTTTGGT
TATTCTAAAAAGCCGGTCTCTTGTAGCTACTAGTCGAAAATCAAATGAGGGTTATTACAGTAGTT
TAAATGCTGATCAAGCCACGAGGATGATTAGCTATATTAAACAACCAATCAATTGTCAGTACCTTT
AATTATTTCAAAAGTCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/94 (serotype 1); SEQ ID NO: 161
GAAGAGTATTCTGGTAACTGCTAACGATGGATTGCCCTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
ATGCTAAAGAAGTGTCCCTGCGCTCAGTCAGTAAGCTCTTGACAAACCTATCTGGTTACAAAGAAGTTTC
TAAGGCGAACGTTAATTGGGATAGCTGTAACTATTCTAACTACCCCTATGAACTCACTACAAACTATAC
40 ATTAGTAACGTTCTCTTGTATAAGAAAATACCGTTAAAGAACTTTAAGTGGCTTAGTGTATAACG
CCAATAGCCCCGTTAGTCTTAGCTGAGAAAATAGGCGGAACCGAACCCAAATTGTTGACAAAATGAAAAA
ACAATTAAAGGCAATTGGGCAATTCCGATGCAAAGGCTGCTAACTCAACTACCAATTTTTGTAG
GCTAATACCTATCTTAAAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGCTGGACAAAC
GGCATCTTATTAGAATTCCAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGCTGGACAAAC
55 CATTCTAACGTTAATTACATGCTTAAAGGCATGCCCTGTATCGAGAAGCGTGGATGGCTTTGGT
TATTCTAAAAAGCCGGTCTCTTGTAGCTACTAGTCGAAAATCAAATGAGGGTTATTACAGTAGTT
TAAATGCTGATCAAGCCACGAGGATGATTAGCTATATTAAACAACCAATCAATTGTCAGTACCTTT
AATTATTTCAAAAGTCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/142 (serotype 83); SEQ ID NO: 162
50 GAAGAGTATTCTGGTAACTGCTAACGATGGATTGCCCTGACCTTGAAGTGGCAAAGTTTATACGAAAAAG
ATGCTAAAGGAGTGTCCCTGCGCTCAGTCAGTAAGCTCTTGACAAACCTATCTGGTTACAAAGAAGTTTC
TAAGGCGAACGTTAATTGGGATAGCTGTAACTATTCTAACTACCCCTATGAACTCACTACAAACTATAC
ATTAGTAACGTTCTCTTGTATAAGAAAATACCGTTAAAGAACTTTAAGTGGCTTAGTGTATAACG
CCAATAGCCCCGTTAGTCTTAGCTGAGAAAATAGGCGGAACCGAACCCAAATTGTTGACAAAATGAAAAA
60 ACAATTAAAGGCAATTGGGCAATTCCGATGCAAAGGCTGCTAACTCAACTACCAATTTTTGTAG
GCTAATACCTATCTTAAAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGATGGACAAAC
GGCATCTTATTAGAATTCCAGAAGTACTGAAATTATCTAGCAAATCTCCACTATTTTGCTGGACAAAC
CATTCTAACGTTAATTACATGCTTAAAGGCATGCCCTGTATCGAGAAGCGTGGATGGCTTTGGT
TATTCTAAAAAGCCGGTCTCTTGTAGCTACTAGTCGAAAATCAAATGAGGGTTATTACAGTAGTT
TAAATGCTGATCAAGCCACGAGGATGATTAGCTATATTAAACAACCAATCAATTGTCAGTACCTTT

AATTAATTTCAGGAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/144 (serotype 76); SEQ ID NO: 163
GAAGAGTATTGCGTAACGTCTAACGATGCGATTGCCGTTACCTGAAAGTGGCAAAGTTTATACGAAAAAG

- 5 ATGCTTAAAGAAGTTGCCCTGTCAGTCAGTCAAGCTCTTGACAACCTATCTGGTTAACAAAGATTTC
TAAGGGCAGACTAAATGGGATAGTCCTGTAACCTTCTTAACCCCTTATGAACTCACAAACACTAA
ATTAGTAAGCTTCTCTGGTAGAAGAAAATACCGCTTAAAGAACCTTAACTGGCTTAGTTGTTAACAGC
CCAATAGGCCCGCTATTGCTTGTAGCTAAAAAAATAGGCCGAACCCAACTTAACTGGCTTAACTGG
ACATAATAGAACAGGGCTATTCCGATCAGCAAGGTGCTCAATTCACTAACGCTTAACTAACATTCTT
10 GCTAACTATTCTTAATCAGAccagaTGATGAAAATTGTTTGCCTACTGATTAGCTTATTGCA
GGCCTCTTATTAGAATTTCGAGACTGAAATTATCTGAAACCTTCAACTTTTGATGGCAAACAA
CATTTACAGTTATAATTACATGCTTAAAGGCCGCTTGTGTTCTGAGAACGGCTGGATGCTTCTT
TATTCTAAAAAGCGGGTGTCTTTGTAGCTACTGTCGAAATCAAATGAGGGTTAACAGTAGTT
15 TAAATGCTGATCAAAGGCCAGGATGATGCTTATTTAAACACCAATCAATTGTCAGCTACCTT
AATTAAATTCTTAAAGCTGGTAAATTGAA

> Spy0292-3 / Schmitz 1/194 (serotype 44); SEQ ID NO: 164
GAAGAGTATTGCGTAACGTCTAACGATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTATACGAAAAAG

- ATGCTAAAGAAGTTGCCCTCGCCTCAAGTCAGTAAAGCTTGACAACTTATGTTTCAAAGAACGGTT
 20 TAAGGCGCAGCTTAATTGGGATAGTCTGTAACTTCTTAACACTTCTTAACTGAACCTAACTAACATACT
 ATTAGTAACGCTTCTTGTAAAGAAAAATTAACCCCTTAAAGAACCTTAACTGGCTTAGTTGTTAAATCCA
 CCAATAGCCCCGCTATTGCTTAACTGGCCAGCCGACCCAAATTGGTACAAATGAAA
 25 ACAAATAGAACATGGCCATTTCGATGCAAGGTCTCAATTCACTGCTTAACTAACATTCTTGTAGGAA
 GCTAACTATCTTAACTACAAGAACAGATGATGAAAATTGTTTGCCTGCACTGATTAGCTTATTGCCC
 GCATCTTATTAGATAATTCCGAAAGACTGAAATTATCTAACCAAATCCTCCACTATTGTTCTGGAAACAG
 CATTTCAGCTTAACTACATGCTTAAAGGCCATGCCCTGTGTTGAGGAGCGCTGGATGCTTCTTGTGTT
 TATTCTAAAAGGCCGTGCTTCTTTGTAGCTACTAGTGTGCAAAATCAAATGAGGGTTAACAGTAGTT
 30 TAAATGCTGATCAAAGGCCAGGAGTAGTATGCTTAACTAACACCAATCAATTGTCAGTACCTT
 AATTAAATTCTTAAAGTCGCTTAACTGAA

8-241-63

3.1 Full length Spu0416A

35 -> Spw0416A / SE370 (secretary 11; SEQ ID NO: 165)

35 > SpyUW1 / SF701 (serotype 17) SEED ID: No. 165
GGCATATGAGCTAACACATGAGCCGAAACCACATCACGAACTCACGCTCACACAAAGCGAACATCTACCA
ATACAGATTGAGGCTCAGCTGAATCTAAACATCTCAAGACACATCACAAATCACTCTAACAGAACATACTGGTAA
AGACCAATCAACAAAGATCTAGTCCTGAGCCACACCACACTGAGCTAGTGACAGATGCGAGCATACAGATTTGAGCT
AATACAGGTTCTGTGAGCTAACAAAAGGCCCTTCTTACCGGAGTCATACAGATGTTGAGCTTGGGTA

- 40 AAACCAAAGGAGCTTGGGACAAAGGGATACAAAGGACAAGGCCAAGGTCTGCAGCATTTGACACAGGTCTGA
TCGGCCCATCAAAAGCTGGCATCTAGTGTATCACTGCTAAAGTAAATCAAAAGAACATGCTAGCA
CCCCAAAAGGCCCGGTATTAAATGGAGGTGTTGAAATGATAAATGATAGTGTGTTTGCACATAATGTTG
AAAATAGGCTATAATCAAAAGAAAATCAATTGAGGATTGTGAGGACTGGGAAACTTGTGAGTTGATG
AGAGGCCAGAGCCCCAAAGGCATCAAAACAGACATCTATGCTCCCAATCACCCAGGCCAAGGAAACT
45 GTTATCAAACAGAACAGAAGAACAGATGGTTCACATGATATGACTGACACAAACAGCATGACCAAATACGG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGTAATGCAAAGAACGCCGCTACTGGAAACGCTT
TTTAGGAATTGCCCCAGGGCCCAAGTCATGCTTCATGCGTCTTGGCCAAACGACATGGGATCAGCTGAA
TCACTCTTATCAACGATCTGAAAGATGCCGCTTGTAGGAGCATGTCATGACAACTGAGCTTGTGAA
50 CTAATGGGCACAGCTTGTGGCAGCAAGGCTTAATGGAAAGCAATTGAAAAGCTAAAAAACGCCGGTTATG
AGTTGTGTGACAGGAAATGGCCGCTATGGATCTGACCATGATGTCATTGGCGACAAATCCAGAC
TATGGTTTGTGCTTCCTCCAAACAGGTGCAACACCATGTCAGGCGCATTAACAGTACTGGT
TTCAACGCTTAATGAGCTAAAGAAATTAGAAAACCGTGGCATTAAACCATGTAAGGCACTTATTGAG
GTCTCTGACTTAAAGACATTAAGAGCATCTGGCTATTGTGATAATCCTGCAATTCTGCTTATGCTAA
55 TCAACTGTCAGGGCTTATAGCCGAACAGCTTAAAGGTTAAATGCTTAAATGCTTAAATGAGCTTGTCA
CCTATGACGAATGATTGCTTGGCTAAGAACATGGAGCTGGGGACTATTATTTAATACAGCCTG
TCATAACACCCGCTAACAGCTTAAAGGATGATGGGTGGGATACATCTGCTTCTATCAGCAGATT
GGTAAGGCCATGCTTCAAAATGGCAATGTCAGCACAGGATTAGGTGACATGCTGCTCAACAGCA
CGAGTCAAAAGGCAATGAATGAATCATTTCATAATTGGGCTAACTCTGATGGCTATTAAAACCTG
CATTACTGCAACAGGCTGGGATCTTATCTACCTTAAAGCATACACTATGGTGGCAAAACGAGGAACAGT
60 ATGGCTCTCTTCAGATTGTGGCCAGGGCTTGTGCAACATACACTTAACTGAGGAAAGCTCACCACACTG

5 CAAAAAGAAAAAAATTGCTGATATCGTTAACCTTATTGATGAGCAATGCTCAAATTCTATGTTAATCCAGAGAC
AAAAACGACCACCTCAGCGTCAGCAAGGGCAGGATTACTTAATATTGACGGAGCTGCCTACTAGGGCCCT
TATGTGACAGAAAAGACACAATCTGCACTATCATAGGCAACATCACAGATAAGCTGACGTTGATGTGA
CTGTTCAACACCTAACGAAATAAGACAAAATTCTAGCTTATGACAGAACAGATCTAACAGATCATGAGACC
10 5 ACAAAAGGGCCCTACTTCACTCTTCACTCTTAAACAGCTTACAGTTCACAGTCAACAAAAGAGCTAACAAAAGACATGCCA
ATGGAAAAGTACTGTAAAGGTTTACATGGATGTCCTACAGTTCACAGTCAACAAAAGAGCTAACAAAAGACATGCCA
ATGGTACTATCTAGAGGTTTGTCCGTTAGAGATAGTCAAGATGACCAACTAATAGAGTAAACATTCC
TTTGTGTTTAAAGGCAATTGAAAACCTAGGATGCAAGAGTCATTACAGATTAAATCTCAA
GGCAAACACTGGTTTACTTGTGATGAATCAGGTCAAAAGACGATATCTATGCGGTAAAACACTTACAGGAC
10 TTGTCATCTTGGTCAGAG

3.2 Antigenic fragment Spy0416A-1

> Spy0416A-1 / SF370 (serotype 1); SEQ ID NO: 14
 15 GCAGATGAGCTAACGACAATGAGCAACCAACATCACGAACTACGGCTAACACAAGGCACACATCTCACCA
ATACAGAGTGGCTGAGCTGAGCTAACAAATCTCAAGACACATCACAAATCCTCAAGACAAATCTGAAAA
AGAGCAATCACAGATCTGAGCTCTGAGCCACACAACTGAGCTAGCTGACACAGATGAGCTAACATGGCT
AATACAGGTCTGATGCGACTAAAAAGGCCCTTCTTACCGCCAGCTCAATACAGATGTTCACGATTGGTAA
AAACCAAGGGCTTGGGACAAGGGATAACAGGACAAGGGCAAGGTGTCAGCTTATTGACACAGGGATGCA
20 TCGCCCCATCAAGCATGGCATCAGTGATGATCAACTGCTAAAGTAAATCAAAGAACAGATGCTAGCA
CGCCAAAAGGCCCGCTTAAATTATGGGAGTTGGATAATGATAAAGTTGTTTGCACATAATTATGTTG
AAAATAGCGATAATCAAGGAAATCATTCAGGAGATTGAGGACTGGGAAAATTGAGTTGATG
AGAGGCAGACCAAAAGCCATCAAAACAAAGCATCTATGTCGCCAATCACCCAGGACCGAAAGAAACT
GTTATCAAACAGAACAGAAACAGATGGTCACATGATGTTACTGAGCACACAGACGATGACCAAAATAG
25 AGTCACAGCTGATGAGCTGAGCGATTGAGCGCTTATGGCCGTTAACGAAAGACGGCTGCTACTGGAGAACGCTT
TTAGGAATTGACCAAGGGCCAAGTCATGTTGATGGCTTGTGCAACGACATCATGGATCAGCTG
TCATCTTTATAAGCATTCAGGAGTGGCGCTTGTAGGAGCAGATGATCAACCTGAGTCTGGTAAACCG
CTAATGGGCCACAGCTTAGTGGCACAGGCTCTAAATGGAGCAATTGAAAAGCTAAAAAGGGCTGTATC
AGTTGTGAGCAGCAGGAAATGAGCGCTCTATGGATCTGACCATGATGATCCATTGGCAGAACATCCAGAC
30 30 TTAGGTTGGCGCTTCTCCCAACAGGTCACACCAACATGAGCGCTATAAAGCATGTTAGGTGAGCTTAAACAGTAAAGGGTGA
TCAACGCTTAAAGGGCTTAAACGGTCTGGGATTAAACCATGTTAGGTGAGCTTAAACGGTCTTAACTTCAAAAG
TCATGATGCGGGTTAAACGAGCTTAAAGGCAACAGCTTAAAGGTTAAATGCTTAAATGAAACGTTGATCCAAATAAA
CCTATGACGAAAATGATTGCTTGGCTAAAGAACATGGAGCTCTGGGAGTACTTATTAAATAACAGCTGG
35 35 TCAATCAAACCCGCTCAATGGCTTCAACAGCTAATGGGATGGGATACCATTGCTTCTATCTGCAAGGAATT
GGTAAGGCCATGTCCTAAATTAGGCAATGGTCAAGGAGTTGAGTTGACAGTCTGGCTCTCAAAGAC
CGAGCTTAAAGGCAATGAAATGATCATTCTTCAAAATTGGGCTCAACTCTGATGCTTATTAAACACTG
CATTAGCACCAGTGGCCTATCTTCACTTAAACGATAACCAACTATGGTAGGCAAACAGGCAACAA
ATGGCTCTCTCAGATGCTGGCGCCAGCTTGTGGCTAAACAAATCTGAGGAAAGACTCAGGCAAATTG
40 CAAAAGAAAAAAATTGCTGATATGTTAAAGACCTATTGATGAGCAATGCTCAAATCATGTTAATCCAGAGAC
AAAACGACCACCTCACCGCTCAGCAAGGGCA

3.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

45 > Spy0416A-1 / Schmitz 1/7 (serotype 4); SEQ ID NO: 166
 GCAGATGAGCTAACACAAACAGAGTGAACCAACATCACGAACTACGGCTAACACAAGGCACACATCTCACCA
ATACAGAGTGGCTGAGCTGAGCTAACAAATCCAGACACATCACAAATCCTCCAAAGACAAATCTGAAAA
AGAGCAACACAAAGCTTAGCTCTGAGCCACACAACTGAGCTAGCTGACACAGATGAGCTAACATGGCT
AATACAGTCTGATGGGACTCAAAAAAGGCCCTTCTTACCGCCAGTCATACAGATGTTCACGATTGGTAA
50 AAACCAAGGGAGCTTGGACAAGGGATAACAGGACAAGGGCAAGGTGTCAGTGTGATCAACTGCTAAAGTAAATCAAAGAACATGCTAGCA
TCCGGCCCATCAAAGCATGGCATCAGTGATGATCAACTGCTAAAGTAAATCAAAGAACATGCTAGCA
CGCCAAAAGGCCGGCTTAAATTATGGAGATTGAGATAATGATAAAGTTGTTTGCACATAATTATGTTG
AAAATAGCGATAATCAAGGAAATCATTCAGGAGATTGAGGACTGGGAAAATTGAGTTGATG
AGAGCCAAGGCAATCAAACAAAGCATCTATGTCGCCAATCACCCAGGACCGAAAGAAACTGTTATC
55 AAAACAGAACAGGAAACAGATGGTCACATGATGTTACTGAGCACAACAGACGAGTACACCCAATACAGTAC
ACGGTATGCTGAGCTGAGCTTATGGCCGTTAACGAAAGAACGGCTGCTACTGGAGAACGCTTATTAGG
AATTGCAACAGGGCCCAAGTCATGTTGATGGCTTGTGCAACGAGCTCATGGGATCAGCTGAATCACTC
TTTATCAAAGCTATGCAAGGAGCTGCTTGTAGGAGCAGATGATCAACCTGAGTCTTGGAAACCGCTAATG
GGCACACGCTTAGTGGCACAGGCTCTAAATGGAGCAATTGAAAAGACTAAAGGGCTGTATCAGTGT
60 TGTAGCAGCAGGAAATGAGCGCTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGACTATGGT

TTGGTCGGTTCTCCCTAACAGTCGAACACCAACAACTCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAC
GCTTAATGAGGCCAAAGAATTAGAAAACCGCTGGCATTTAACCTATGTAAGGCATCTATTCTAGACTCTG
CGActttaaaagactaaaagatcgcttaggttatgataaATCGCATCAATTGCTTATGTCAAAGTCAGTCACT
GATGCGGTATAAACGACAAGACGTTAACAGATAAAATTGCTTAAATTGAACTGATCCAAATAAAACCTATG
5 ACGAAATGATTGCTTGGCTAAAGAACATGGAGGCCCTGGAGTACTTATTTAATAACAAAGCTGGTCATTC
AAACCCCTCAATGCTCAACAGCTAATGGATGGGATACCATCTGCTTTCATATCGCACGAATTGGTAG
GCCATGCTCCAATAAGGCAATGGTACAGGAAGTTAGAGTTTGACAGTGTGGCTCAAGACGCCAGGTC
AAAAAGGCAATGAAATGAATCATTTTCAATTGGGCCCTAACCTCTGATGGCTATTAAACCTGACATTAC
10 TGACCAAGCTGGCAGATCTACTCTACCTAACGATAACCAACTATGTTAGCCAAACAGGAACAGTATGGC
TCTCCCTAGATTGCTGGCTTGGCTAAACAAATCCAGAAAAGACTCAGGCCAAACTGGCTTAAAG
AAAAAATTGCTGATATGTTAAAGACCTTATGTGAGCAATGCTCAAATTCTGTTAACCCAGAGACAAA
GACCACCTACCGCGTCAGCAAGGGCA

> Spy0416A-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 167
 15 GCAGATGAGCTAACACAAACGAGTGAACCAACAACTCAGAATCACACTCACAAACAAAGCCACATCTCACCA
ATACAGAGTGGCTGAGCTGAGCTAACAAACCTAACAGACACATCACAAATCCTCAAGACAAATCTGAAAA
AGAGCAACCAACAGCTACTCTGAGCCAAACCAACTGAGCTGAGCTGACACAGATGCGCACCAATGGCT
AATACAGTCTGATGGCTCAAAAGGCCCTTTCACCGCCAGTCATACAGATGTTGACAGTGGTGG
AAACCAAAAGGCTTGGCAACGGGATAACAGGAAAGCAGGAGTGTGCGAGTTATGACACAGGGATCGA
20 TCGGGCCATACAGGATGCGCATCAGTGTATCACTGCTAACTGTTAAAGTAAAGTAAATGTTTGCACTAATATTGCG
CGCCAAAAAGGCCCGGTATAATTATGGAGATGGATAATGAAAGTTGTTTGCACTAATATTGCG
AAAAATAGCCATAATTAACAGGAAATCATTCAGGAGTTGATGGAGGACTGGGAAACTTITGACTTTGATG
AGAGGCAAGGCCAAACAGCTAACAAACAAAGATCTATGCTCCCAATCACCCAGGCCAAAGAAACT
GTTTACAAAACAGGAAACAGGATGGTTCACATGATGATGACTGAGCACAACAAAGCAGATGACACAAA
25 ACTCACCGGTTGATGCTGACGGTTATGAGCCGTTAATAGCAGAACGCCGTGCTACTGGAGAACGCTT
TTTGGAGATTGACCAAGGCCCCAAGTCATGTTCATGGTTTTTGGCAACAGCGCTCATGGGATCAGCTGA
TCACTTTTAACTAACAGGATCTAGCGAGATGGCGCTTGTAGGAGCAGATGATCAACCTGAGTCTGG
CTAATGGGACAGCTTAGTGGCACAGGCTCTAAATGAGGCAATTGAAAAGCTAAAGGCCGGTGTATC
AGTTGTTAGCAGCAGGAAATGAGCGCTATGATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGAC
30 TTATGGTTGCGGTTCTCCCTAACAGGTCGAACACCAACATGTCAGGCTATAAACAGTAAGTGG
TCAACGGCTTAATGACGGTCAAAGATAAGGACCTGGGCAATTGAGGATTAACCATGTTAAGGCT
GTCGICGActttaaaGACATAAAGATGCTAGGTTATGATAATTCGCTCAATTGCTTATGTCaAGAG
TCAACTGATCGGGTTAAACGCAAGGCTAAAGGTTAAAGGTTAAATTGAGCAGTGGCACTTAAAGG
35 CCTATGACGAAATGATTGCTTGGCTAAAGAACATGGGCTGGGACTTATTTTAAATTAACAGCCTGG
TCAATCAACGGCTTAACGGCTTAACAGCTAATGGATGGGATACCATGCTTTCATATCGCAGCAATT
GGTAGGCCATTGTCCTAACATTGGCAATGGTAGCGGACTTAAAGGCTATACTGGCAGTGG
CGACTAAAGGGCAATGAAATGATCATTTCAAAATTGGGCCCTAACCTGATCTGTTGCTCAAAAGC
CATTAATGACCGAGGTGGCCGATATCTACTCTACCTATAACGATAACCAACTATGGTAGCCAAACAGGA
40 CAAAGAAAAAAATTGCTGATATGTTAAAGACCTTATGTGAGCAATGCTAAATTCTGTTAACAG
AAAAACGACCAACCTACCGCGTCAGCAAGGGCA

> Spy0416A-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 168
 GCAGATGAGCTAACACAAACGAGTGAACCAACAACTCAGAATCACACTCACAAACAAAGCCACCTCTCACCA
 45 ATACAGAGTGGCTGAGCTCACAAACCAACTAACAGACATCACACTAACAGATGCGCACCAATGGCT
AATACAGGTTGATGGCTCAAAAGGCCCTTTCACCGCCAGTCATACAGATGTTGACAGTGG
AAACCAAAAGGAGCTGGCAACGGGATAACAGGAAAGCAGGAGTGTGCGAGTTATGACACAGGGATCGA
TCCGGCCATACAGCATGCGCATCAGTGTATCACTGTTAAAGTAAATCAAAGGAGACATGCTAGCA
50 CGCCAAAAAGGCCGGTATAATTATGGAGATGGTAATGATAAAAGTTGTTTGACATAATTATGCG
AAAATAGCGATAATATCAAAGGAAATCAATTGAGGATTGATGGAGCTGGGAAACTTGTGAGTTGATG
AGAGGAGAGGCCAAAGGCTAACAAACAAAGATCTGTCATGATATTGACTGACACAAACAGCAGATG
GTTTACAAAACAGGAAACAGGATGGTTCACATGATATTGACTGACACAAACAGCAGATGACACAAA
AGTCACACGGTTGATGCTGACGGTTATGAGCGGTAAATGAGGAAAGGCCGTGCTACTGGAGAACGGT
 55 TTGAGGATTGACCGAGGGCCAAAGTCATGTTGATGGCTTGTGAGGAGCTGATCAACCTGACTTGG
TCATCTTAAACAGGCTATGCGAGATGGCTGGCCCTAACAGGAGCTGATCAACCTGACTTGG
CTAATGGGCCACAGCTTAGTGGCACAGGCCCTAACAGGAACTGAAAGCTAAAGGCCGGTGTATC
AGTGTGTTGAGCAGCAGGAAATGAGCGCTCTATGGATCTGACCATGATGATCATTGGC
TATGGTTGGCGTCTCCCTAACAGGCGAACACCAACATCAGTAGCAGCTATAAACAGTAAGTGGTGA
60 TTCAACGCTTAATGACGGTCAAAGATAAGGAAACCGTGGCATTAAACCATGTTAACCGCATCTaTTGAGA

GTCTGTCGACTTTAAAGACATAAAAAGATAGCGTAGGTATGATAAATCGCATCAATTGGCTATGTCaaAGAG
TCAACTGATGGGGTTAACGCAAAAAGCTTAAGGAAATTGCTTAACTGGAGCTGGAGTACTTATTAAACAGCCTGG
CTTATGACGAAAATGATGTTTGCCTAAGAACATGGACCCCTGGAGTACTTATTAAACAGCCTGG
TCATCAAACCGCTAACAGCTAATGGGATGGGGACATCCATGGCTTCAATTGCGCAACTTGA
5 GGTAAGGCCATGCCAATTAGGCAATGGTACAGGAATTAGCTTAACTGGGCTAACCTCTGATGGCTATTAAACCTGA
CGAGTCAAAAGGCAATGAAATGATTCATTCAAAATTGGGCTAACCTCTGATGGCTATTAAACCTGA
CATTAGCACCAGGTGGCGATATCTACTCTACCTTAACGATAACCAACTATGGTAGGCAAACAGGAACT
ATGGCTCTCCCTCAGATGCTGGGCCAGCTTGGTCAAACAACTAGAAAAGACTCAGGAAAATTG
10 CAAAAGAAAAATTGCTGATATGCTTAAAGACCTATTGATGAGCAATGCTCAAATTGATTTAATCCAGAGAC
AAAAAGCACCACCTCACCGCTCAGCAAGGGCA
> Spy 0416A-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 169
GCAGATGAGCTAACGCAACAGGCTGAAACACGCTAACACAAGGCCAACATCTCACCA
ATACAGAGTTGAGCTCAGTGAATCACAATCCCAGACATCACAACTCTCAAGATAATCTGTA
15 AGAGCAACACAAAGGCTAGTCTGAGCCAACCACAACTGAGCTAGTGCACAGAGCAGCACCACATGGCT
AATACAGCTGATGGCTAACAAAGGCGCTTCTTACGGCCAGTCATACAGATGTCAGATTGGTAA
AAACCAAGGAGCTGGCAAAAGGCTACAAGAGCAAGGTTAGGCTTATGACACAGGGCTAGCA
TCCGGGCCATCAAAAGCATGGCCATCAGTGATGATCAACTCTAAAGTAAATCAAAGAACATGCTAGCA
CGCCAAAAGGCCGGTATAATTATGGAGGTGGATATAATGATAAAGTTGTTTGCACATTAATTATGCG
20 AAAATAGCTGATAATCAAAAGAAATCACTGGAGATTGATGAGACTGGAAAATTGAGCTTGTG
AGAGCCAAGGCTAACAAAACACAAGTATCTGCTCCCAATGCAACCCAGGCAAAAGAAACTGTTATC
AAAACAGAAGAACAGATGGCTCATGATATTGACTGGACACAAACAGCGATGACACCAAACTCAGACTC
ACGGTATGCTGAGCAGTATTGAGCCGTTAATGAAAGAAGCCGCTACTGGAGAACGCTTTAGG
AATTGACCAAGGACCAAGCTGATGCTGAGCTGGTTTGCACAGCTATGGGATCAAGACTTAC
25 TTATACAAAGCTATCGAGATGGCTGGCTTACGGAGCATGATGTCACACTGAGCTTGGGACCCGCTAATG
GTGACAGCTAGTGGCAGCAAGCCTTAATGAAAGCAATTGAAAAGCTAAACCCGGTGTATCAGTGT
TGAGCAGCAGGAAATGAGGGCTCTAGTGGATCTGACCTATGATCATTGGCAACAAACTCAGACTATGG
TTGGCTGGTTCTCCCTCAACAGGCTGAAACCAACATCAGTGGCAGCTATAAACAGTAAGTGGTGTAC
30 GTCTAATGAGCTAACAAAGATTGAAAACCGTGGCGATTAAACATGGTAAAGGCCATCTaTCAGACTCT
CGACTTAACAGATAACGCTACCTGGTATACTGATAAATGCGCATATTGGCTTATGCAAAAGACTCA
GATGGGGTTAACGCAAAAGCTTAAAGTAAAATGCTTAAATGAACTGATCCCAATAAACCTATG
ACGAATGATGCTTGGCTAAGAAACATGGAGCCCTGGAGTACTTATTAAATAACAGCCTGGCTAAC
AAACCGCTAACAGCTAACAGCTAACAGGATATGGGATGGGACATCCCTGCTCATTCGACAAATTG
35 GGCATGCTAACAAAGGAGCTTGGGACAAGGGATCAAGGACAAGGCAAGGTTAGGTTGAGCTGCTCA
AAAGGCAATGAAATGATTTCAAAATTGGGCTAACACTCTGATGGCTATTAAAACCTGACATT
TGCAACAGGGGTGATATCTACTCTACCTAACGATAACCAACTATGGTAGGCAAAACGGAACAGTATGCC
TCTCTCAGATTGCTGGGCCAGCTTGGTCAAAACAACTAGAAAAGACTCAGGCCAACCTGGCA
AAAAAATTGCTGATATGCTTAAAGACCTATTGATGAGCAATGCTCAAATTGATTTAATCCAGAGACAAA
GACCACCTCACCGCTCAGCAAGGGCA
40 > Spy 0416A-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 170
GCAGATGAGCTAACGCAATGAGGCCAACAACTCAGGAATCAGCTAACACAAGGCCAACATCTCACCA
ATACAGAGTTGAGCTCAGTGAATCACAATCTCAAGACACATCACAACTCTCAAGACAACTCTG
AGAGCAACACAAAGGCTAGTCTGAGCCAACCAACATGGAGCTAGTGCACAGAGCAGCACAATGGCT
45 AATACAGGTTGAGCTGGCCCTTAAAGGCGCTTCTTACGGCCAGTCATACAGATGTTGACAGTGGTAA
AAACCAAGGAGCTTGGGACAAGGGATCAAGGACAAGGCAAGGTTGTCGAGTTATGACACAGGGATCGA
TCCGGCCCATCAAAAGCATGGCCATCAGTGATGATCACTCTAAAGTAAATCAAAGAACATGCTAGCA
CGCCAAAAGGCCGGTTAAATTATGGGAGTTGATGAAATTGATGAGCTGGAAAATTGAGTTG
50 AAAATAGCGATAATATCAAAGAAATCATTCAGGAGTTTGATGAGGACTGGAAAATTGAGTTG
AGAGGCCAGGCCAACAGCTAACAAAACACAAGATCTATGCTCCCAATCACCCAGGCCAACAG
GTTATCAAAACAGAAGAACAGATGGTTCACATGATATTGAGCTGGACACAAACAGCGATGACACCAAAATGCC
AGTCACACGGTATGCTGAGCTGGATTAATGGAGCCGTTAACAGGCTACTGGAGAACGCTT
55 TTTAGGAAATTGACCAAGGCCAACAGTCTGATGGCTTGGCTTGGCAACGACATCATGGGATCAGTGA
TCACCTTTATCAAAAGCTATCGAGATGCCCTGGCTTGGAGCAGATGATCACCTGACTTGGAAACCG
CTAATGGGCCAACACCTAGTGGCAGACGCCCTAATGGAGCAATTGAAAAGCTAAAAGGCCGTATC
AGTGTGTTGAGCAGGAAATGCCCTPATGGATCAGCATGATGTCATTGGCCTAACATCCAGAC
TATGGTTGGCTGGCTTCCCTCAACAGGCTGAAACCAACATCAGTGGCAGCTATAAACAGTAAGTGGTGA
60 TCAACTGATGCCGGTTAACGCAAGCGTAAAGGTTAAATTGCTTAAATTGAGCTGATCCCAATA
TTGAGCTTATGCTTAAAGACATAAGAGTAGCTGAGTTGATGATGATGCTAACATTGCTTATGCTGAAAG
GCTGTCGACTTTAAAGACATAAGAGTAGCTGAGTTGATGATGATGCTAACATTGCTTATGCTGAAAG
TCAACTGATGCCGGTTAACGCAAGCGTAAAGGTTAAATTGCTTAAATTGAGCTGATCCCAATA
AA

- CCTATGACGAATGATTGCTTGGCTAAGAACATGGAGCTCTGGAGTACTTATTTTAAATAACAGCCTGG
TCAACAAAGCTCAATGCCTCAACAGCTAACAGCTAACATGGGGATACCATCGCTTCATATCGCACGAATT
GGTAAGGCCATGCCAATTAATGGCAATGGTACAGGAAGTTAGAGTTGAGCTGTGCTCTCAAAGCAC
CGAGTCAAAAGGCAATGAATGAATCATTTTCAATTGGGCTAACCTCTGATGGCTATTTAAACCTGA
5 CATTACTGACCGAGTGGCAGATCTTACCTAACATGGCAACACCAACTGGTACGCCAACAGGAACAGT
ATGGCCTCTCTCAGATTCGCCCCAGCTTTGGTCAAAACATACCTAGAAAAGACTCAGCCAACACTGC
CAAAGAAAAAAATTCGTAATCTGTTAAAGAACCTATTGATGAGCAATGCTCAAATCATGTTAATCCAGAGAC
AAAAAGACCACTCACCGCGTCAGCAAGGGCA
- 10 > Spy0416A-1 / Schmitz 1/253 (serotype 49); SEQ ID NO: 171
GCAGATGACCTAACACAAACAGTGAAACAAACATCGAACTACGCTCAACAAACAGCGAACACTCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCACAACTCCCAGACATATCACAGTAACCTCAGAGAACATCGTAAAGA
AGAGCAACAAAGGCAAGCTAGCTCTGAGCAACAAACAGCTAGCTGACACAGATGAGCACACAACTGGCT
AATACAGGTCTGATGCCATGAAAGCTTAAAGGGCTTCTTACCGCAGTCAATACAGATGTTCACGATTGGTAA
15 AAACCAAAAGGAGCTGGGACAAGGGATAAAAGGACAAGGCAAGGGTTGCGCAGTTATGCAACAGGGATCCA
TCGGCCCATCAAAAGGCTAGCGGCTCATGAGTCTAACAGTCTAACAGTAAAGTCAAAAGGAGACATGAGCA
CGCCAAAAGGCGCCGTTAATTAATGGGAGTTGGATAATGATAAAAGTGTGTTTGCACATAATTATGG
AAATAGCGATAATCAAAAGAAAATCAATTGGGAGTTATGAGGACTGGGAAAACTTTGTGTTGATGTC
20 AGATGCAAGGCCAACAGCATCAAAAGAACAAAGATCTATGCTCCCAATCAACCCAGGCCGAAAGAAAAT
GTATCATACAAAGAACAGATGTTCAATGATTAGCTGGACAAACAGACATGACACAAATACG
AGTCACAGCTATGCTGTGACAGTTGAGCGCTTAGCAGTCTAACAGGAGCGCTACTGGAGAACGCTT
TTAGGAATTGACCGAGGGCCAAGTCTAGTGTCTAGCGCTTTTGCACAGCGTCATGGGATCAGTGA
TCACCTTATCAAGCTATCGAAAGATGCCGCTTAAAGGAGCAGATGTGATCAACCTGAGCTTGTGAAACCG
CTAATGGGCAAGCAGCTAGTGGCAGAACGCTTAAAGGAACTTGAAGGAAACCTGGGCAAGCTGTATC
25 AGTTGTTGAGCAGGAAATGGCCGCTCATGATCTGACCATGATGATCATTGCAACAAATCCAGAC
TATGGTTGTCGGTTCTCTAACAGGTCGAACACCAACTAGTGGCAGCTATAAACAGTAAGTGGTGA
TTCAGCTCTATAGCGCTAAAGGATGAAAAGGCGCTGGGCTATAACATGGTAAAGGCCATCTTATCGA
GTCTGTCGACTTTAAAGACATAAAAGATAGCTGTTAGGTTATGATAATGCGCATCAATTGCTTATGTCAAAG
30 TCAACTGATGGGGTTAAACGACAAGCTTAAAGGTTAAATGCTTAAATGAGCTGATCCAAATAAA
CCTATGACAAAGGATGCTTGGCTAACGAAATGGGCCCTGGGACTACTTATTAAATAACAGCTGG
TCACATCAACCCGCTCATGGCTCAACAGCTAACAGGCTGGGACTTAAAGGAACTTAAACAGCTGG
GGTAAGGCCATGCCAATTAATGGCAATGGTACAGGAAGTTAGAGTTGAGCTGTGGCTCAAAGCAC
CGAGTCAAAAGGCTATGAAATGAATCTTCAATTGGGCTAACCTCTGATGGCTTAAACCTGA
35 CATTACTGACCGAGTGGCAGATACTACCTAACATGGCAACACCAACTGGTACGCCAACAGGAACAGT
ATGGCCTCTCTCAGATGCTGGGGCAGCTTTGGTCAAAACATACCTAGAAAAGAACCCAGGCCAAACTGC
CAAAGAAAAAAATTCGTAATCTGTTAAAGAACCTATTGATGAGCAATGCTCAAATCATGTTAATCCAGAGAC
AAAAACACCACTCACCGCGTCAGCAAGGGCA
- > Spy0416A-1 / Schmitz 1/174 (serotype 6); SEQ ID NO: 172
40 GCAGATGACCTAACACAAACAGTGAAACAAACATCGAACTACGCTCAACAAACAGCGAACACTCTCACCA
ATACAGAGTTGAGCTCAGCTGAACAAACCTAACAGACATCACAAATCCTCCAAAGACAAATCTGGTAAAGA
AGAGCAATCACAAAGATCTGCTCTGACCAACACAACTGAGCTGAGCTGACACAGATGCGCATCAATGGCT
AATACAGGTCTGATGCGACTCAAAAGCCTTCTTACCGCAGTCAATACAGATGTTGAGCTTGGTAA
AAACCAAAAGGCTTGGCAAGGGATAAAAGGACAAGGCAAGGGTTGCGCAGTTATGACACAGGGATC
45 TCCGGCCATCAAGCATGGCATCAGTGATGATCTAACCTGAAAGTAAATCAAAGGAGATGCTAG
CGCCTTAAAGGCGCGTATTAAATTGGGAGTTGGATAATGATAAAAGTGTGTTTGCACATAATTATGTGG
AAAATAGCGATAATCAAAAGAAAATCAATTGGGAGTTGGATGAGGACTGGGAAAACCTTGTGTTGATGTC
AGAGGCCAGGCCAACAGCTAACAAAACAAAGATCTATGCTCCCAATCAACCCAGGCCAAAGAAAACT
GTTATCAAAAGAAGAACAGATGGTICACATGATATGACTGGACACAAACAGACATGACACAAATACG
50 AGTCACAGCTATGCTGTGACAGGTTATGAGCGCTTAAAGCAAGGAGCGCTGCTACTGGAGAACGCTT
TTAGGAATTGACCGAGGCCAACGCTATGTTCTAGCGTTTGCACAGCGCTATGGGATCAGTGA
TCACCTTATCAAGGCTATGAGGCTGGCTTAAAGGAGCAGATGTGATCAACCTGACTCTGGAAACCG
CTAATGGGCCAGCTTAGTGGCAGCACGCTTAAAGGAACTTGAAGGCTTAAAGGCTTAAAGGCCGTGATC
AGTTGTTGAGCAGGAAATGAGCGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAG
55 TATGGTTGGTGGCTTCTCCCAACAGGTCAGCAACACCAACATGAGGCAAGCTTAAAGGAGCTTAAAGGAGCTT
TTCAACCTCTAATGAGCTCAAGAATTGAGGCTGGGATTTGGGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTT
GCTCTGTCGACTTTAAACATAAAAGATAGCTGAGTTGATAATGCGCATCAATTGCTTATGTCAAAG
TCAACTGATGGGGTTAAACGCAACAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAGGAGCTTAAAG
CCTATGACGAATGATGCTGGCTAACATGGGAGCTGGGAGTACTTATTTTAAATAACAGGCAACACTGG
60 TCAATCAACCCGCTCATGGCCTAACATCAATGGGAGTGGAAATACCATGCTTATCGCTTATGCGACGAATT

GGTAAGGCCATGCCAATTAAATGGCAATGGTACAGGAAGTTAGAGTTGAGCTGGCTCTAAAAGCAC
CGAGTCAAAAGGCAATGAATACTTTCAATTGGGCCAACTCTGATGGCTTTAAACCTG
5 CATTACTCACCAGGTGGCATATCTACTCTACCTAACGATAACCCATATGGTAGCCAACAGGAACAGT
ATGGCCCTCCTCAGATTGCTGGCCGCAGCCTTTGGTCAAACAAATACCTAGAAAAGACTCAGGCCAACATTG
CAAAGAAAAAAATTGCTGATATCTGTAAGAACCTATTGATGAGCAATGCTCAAATTCTATGTTAACCCAGAGAC
10 AAAACGCCACCTCACCGTCAGCAAGGGCA
> Spy0416A-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 173
GCAGATGAGCTAACACAACAGGTGAAACCAACATCACGAATCACACTCAACAAAGCGCAACATCTCACCA
15 ATACAGGTGGCTGAGCTGAGTCAAACCAACAGACATCACAACTCTCAAGACAAATCTGAAA
AGAGCAACCAACAGGTCTAGTCTGAGGCCAACCAACACTGAGCTGACAGATGCGACAGCAACATTGCT
AATACAGGTCTGAGTGCAGTCAAAAAAGCGCTTACCGCAGTCATACTAGATGTTCACGATTGGTAA
AAACCAAAAGGAGCTTGGCAAGGATACAAAGGCAAGGTGTCAGGATTCAGGAAAGTGTGCGAGTTGACAGGATCGA
15 TCCGGCCATCAAGCATGGCCTAGTGATGATTAACCTGCTAAAGTAAATAACAAAGAACATGCTGCA
CGCCAAAAGGCCGGTATTAAATTGGAGTTGGATAATGATAAGTTGTTTGCACATAATTATGTTG
AAAATAGCGATAATCAAAAGGAAATCAATTGGAGTTGGTGTAGGAGCTGGGAAACTTTGAGTTGATGC
20 AGAGGCAGGCCAACAGGCTCAAAACACAGATCTATGCTCCCAACCAACCCAGGCCAGGAAAGAAAC
GTTATCAAAACAGAAGAACAGATGGTCACTGATATTGACTGAGCACAAACAGACGATGACCAAAATACG
TTGACACCGGTATGATGTGAGCTGAGTGTGAGCTGGCTATGAAAGGCAAGGCTGTACTGGGAACAGCTT
25 TTAGAGATTGCCCCAGGCCCCAGTCATGTTCATGGCTTTTGGCACAGCTGATGGATCAGCTGAA
TCAGTCTTATCAAAGCTATGAGATGGCTTGGCTTATGGAGCAGATGTGATCAACCTGAGTTGATGC
CTAATGGCAGCAGCTTGGCTATGGAGCAGGCCCTAATGGAACTTGTGAAAAGCTTAAAGGGCTGTGATC
AGTTGTTAGCAGGCCAATGGAGCTGGCTCTATGGATCTGACCATGATGATCCATTGGCACAAATCCAGAC
30 TAGGTTTGGCGGTCTCCCTAACAGCTGCAAGCACACCAACATGCTGGAGCTATAAACAGTAAAGGGTGA
TTCAACCTTAATGAGCCCAAAGGAAATTGAGAACCTGGCTGGTAAACCATTTGATGAGCAATGCTTATTCAGA
GTCCTGCACTTAAACATAAAGATGCTCTAGGTATGATAAATGCTCAATTGCTTATGCTAAAGAG
35 TCAATGATGGCGGTATAAAGGCAACAGGCTTAAAGGCTTAAAGGTTATGGCTTATGCTAAAGAG
CCTATGACGAAATGATGCTTGGCTAAGAACATGAGGCCCTGGAGTACTTATTAAACAGCTGG
TCATCAACCGCTCAATGCTCTAACAGCTAATGGATGGGATACCATGCTTCTATCGCAGGAATT
GGTAAAGGCCATGCCAATTAAATGGCAATGGTACAGGAAGTTGAGTTGAGCTGGCTTCAAAAGGC
CGAGTAAAAGGCAATGAAATGATCATTTCAAAATTGGGCCATACTCTGATGCTTATTAAACCTG
40 CATTACTGACCAGGTGGCATATCTACTCTACCTATAACGATAACCCATATGGTAGCCAAACAGGAACAGT
ATGGCCCTCTCAGATTGCTGGCCGCAGCTTGGTCAAACAAATACCTAGAAAAGACTCAGGCCAACATTG
CAAAGAAAAAAATTGCTGATATCTGAAACCTATTGAGCAATGCTCAAATTCTATGTTAACCCAGAGAC
AAAAACGCCACCTCACCGTCAGCAAGGGCA

> Spy0416A-1 / Schmitz 1/234 (serotype 44); SEQ ID NO: 174
GCAGATGAGCTAACACAATGAGTGAAACCAACATCACGAATCACCTCACCAACAAAGCGCAACATCTCACCA
45 ATACAGGTGGCTGAGCTGAGTCAAACCAACAGACATCACAACTCTCAAGACATACTCCAAAGACAAATCTGAAA
AGAGCAATCACAAAGATCTAGTCTGAGGCCAACCAACACTGAGCTGACACAGATGCGACATCAATGGCT
AATACAGGTCTGAGTGGCTCAAAAGGCCCTTCTGGCCAGTCATAACAGATGTTGAGCTGGTAA
AAACCAAAAGGAGCTGGCAAGGATACAAAGGCAAGGCAAGGTGTCAGGTTTGGACATGGTCAAAGGATCGA
50 TCCGGCCATCAAGCATGGCATCAGTGATGATCACTGCTAAAGTAAATAACAAAGAACATGCTAGCA
CGCCAGTAAAAGGCAATGAAATGATCATTTCAAAATTGGGCCATACTCTGATGCTTATTAAACCTG
55 AAAATAGCGATAATATAAAAGGAAATCAATTGGAGATTGTTGATGAGGACTGGGAAACTTTGAGTTGATC
AGATGCGAGGCCAACAGCATTAAAACACAAAGATCTATGCTCCCAATCACCCAGGCCACGGAAAGAAAC
GTTATCAAAACAGAAGAACAGATGGTTCATGATGATGAGGACACAAACAGACGATGACCAAAATACG
AGTCACCGGTATGCTGACATGTTAGCAGGCTAATGGAAAGAACAGCCGTGCTACTGGAGAACAGCTT
TTAGAGATTGACCAAGAGGCCAAGTGTGATGCTGTTTGGCCAACGACGTCATGGGATCAGCTGA
60 TCACCTTTATCAAAGCTATGAGATGGCTGGCTTGAAGGAGCAGATGATCAACCTGATCTGGAAACCC
CTAATGGGCCACAGCTTGTGCGAGCAGCTCTAATGGAAAGCAATTGAAAAGCTAAACAGGGCTGTATC
AGTTGTTGAGCAGCAGGAAATGAGCGCTTATGGATCTGACCATGATGACCCATTGGCACAAACATCCAGAC
TATGGTTGTTGGTCTCCCTAACAGGTGCAACACCAACATCAGTGGCAGCTATAAACAGTAAAGTGGGTGA
TTCAACCTTAATGAGCCCAAAGGAAATTGAGAACCTGGCTGGGATTAAACCATGTTAAAGCCATCTTCAGA
65 GTCTGCTGCAATTAAAGACATAAAAGGATAGCTGGTATGATAAATGCTCAATTGCTTATGCTCAAAAGG
TCAACTGATGGGGTTATAAGGCAACAGCTTAAAGATAAATTGCTTAACTGTTAATGAGCTGATCCCATAAAA
CCTATGCGAAATGATGCTTGGCTAAGAACATGGAGCCCTGGGGTACTTATTAAACAGCTGG
TCATCAACCGCTCAATGCTCTAACAGCTAATGGGAGTGGGAAACATCTGCTTCTATGCGACAAATT
GGTAAAGGCCATGTCCTAACATTAGGCAATGGTACAGGAAGTTGAGTTGAGCTGGTCTCAAAGC
60 CGAGTAAAAGGCAATGAAATGATCATTTCAAAATTGGGCCATACTCTGATGGCTATTAAACCTG

CATTACTGCACCAAGGGCGGATATCTACTTACCTATAACGATAACCCTATGGTAGCCAAACAGGAACAGT
ATGGCCTCTCCTCAGATTGTCGGCGCACGCCCTTGGTCACAAATATCTAGAAAAGCTCACGCCAACATGGC
CAAAGAAAAAATTTGCTGATATCTGTTAAAGACCTTATGTGAGCAATGCTCAATTGTTAATCCAGAGAC
AAAAACGACCACCTCACCCGTCAGCAAGGGCA

> Spy0416A-1 / Schmitz 1/22 (serotype 4); SEQ ID NO: 175
GCAGATGAGCTAACCCAAACGAGTAAACCAATACGAGATCACCTCAACACAAGGCCAACATCTCACC
ATACAGAGTTGAGCTCAGCTGAATCAACATCCCCAGACACATCACAAATCACTCCTAACAGAACATCTGAAAA
AGAGCAACCACAAAGGCTAGTCTGAGCCAACCACAACGAGTGCAGCTGACACAGATGCAGCATCATGGCT
10 AATACAGGCTGAGCTGAGCTACAAAAAGCGCTTCTTACGCCGCTACATACAGATGAGCTGAGTGGTAA
AAACCAAGGAGCTGGACAAGGAGTACAAAGGAGAACAGGAGTGTGCGAGTTATTGACACAGGGATCGA
TCGGGCCCCTCAAAAGCATGCGCATCAGTGATGATCAGTCAACTGCTAAAGTAAATCAAAAGAGACATGCTAGCA
CGCCAAAAGGCCGGCTTAAATTATGGAGTTGGATAAATGATAAAGTGTGTTTGACATATTATGTC
15 AAAATAGGGATAATATCAAAAGAAAATCAATTCGGGAGATTGTGAGGACTGGAAAACCTTGA
AGAGCCAAAAGGCATCAAAAAAAACAGATCTATCGTCCCCATCAACCCAGGCCACGGAAAGAACCTTGTATC
AAAAGAGAAACAGATGGTCTACATGATTGACTGGACACAAACAGACGATGACACCAAAATACGATTCAC
ACGGTAGTGCATGAGCTATTGAGCCGTAATGAGAACAGGCGCTGCTACTGAGAACCCCTTTAGG
AATTGACACAGGGCCCAAGTCTGATGTTGCTGTTTGGCAACAGCTCATGGGATCATGGTGA
20 CGACTTAAAGGCTAACAGTCAACTGCTGTTAGGGATGAGCTGTTTGGCAACAGCTCATGGTGA
TTTATCAAAAGCTATCGAGATGGCCGTTAGGGAGCAGATGTGACACTCTGAGTTGGACACGGCTAATG
GGCACAGCTTGTGCGAACAGCTTAATGGAAAGCAATTGAAAAGCTAAAAGCGGTGATCAGTGT
TGTAGCAGCAGGAAATGAGCCGCTCTATGGATCTGACCATGATGTCATGGCAACAAAATCAGCATGTT
25 TTGGTGGTTCTCTCAACAGGTCGACACCAACATCAGTGAGCTGATGAGCTTAAACAGTAAAGTGGTGA
CTCAATGAGCCCAAAAGAATTAGAAAACCGTGCCTGTTAAACCCTGGTAAAGGCCATCTATTGAGCTGT
CGACTTAAAGGCTAACAGTCAACTGCTGTTAGGGATGAGCTGTTTGGCAACAGTCA
30 GATGGGGTTATAAACGCAACAGGCTTAAAGATAAATTGCTTAAATGGACAGTGTGACCTTAAACACCTATG
ACGAAATGATTGCTTGGCTAAGAAAACATGGAGCCCTGGAGACTTATTTAATAACAGGCTGGTCATC
AAACCGCTAATGCGCTAACAGCTTAAAGGGATGGGGATACCATCTGCTCATATGGCAGCAATTGGTAAG
GCCATGCTCCAATAATGGCTAACAGTGGTACAGGAATTGAGTTGAGCTGCTCAAAAGCACCGAGTC
AAAAGGCAATGAATGAATCATTTCAATTGGGGCTAACTCTGATGGCTTAAACCTGACATTAC
35 TGCACCAAGGGCGGATATCTACTACATAACGACCAACTATGGTAGCCAAAAGGAGAAGCTATGGC
TCTCTCTGAGTTGCTGGCCGACCTTTGGTCAACAAATCATGGAGAAGACTCAGGCAACTTGGCA
AAAATGGTGTATCTGTTAAAGACCTTATTGATGAGCAATGCTCAATTGTTAATCCAGAGACAAAAAC
GACCACCTCACCCGTCAGCAAGGGCA

3.4 Antigenic fragment Spy0416A-6

> Spy0416A-6 / SF370 (serotype 1); SEQ ID NO: 15
GCAGTTATTGACACAGGATGTCGCCCCATCAAAGGCTGCGCCTATGGTGTATCACTGCTAAAGTAA
40 AATCAAAAGAAGGAGATCTGAGCAGCTAACAGCTTAAATGGGAGGGATGGATAATGATAAAAGT
TGTGTTTGCACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGATGAGGAC
TGGGAAACTTTGAGTTGATGAGCAGGAGCAGGAAAAGCCATCTGCTCATATGGCAGCAATTGGTAAG
GCCATGCTCCAATAATGGCTAACAGTGGTACAGGAATTGAGTTGAGCTGCTCAAAAGCACCGAGTC
AAAAGGCAATGAATGAATCATTTCAATTGGGGCTAACTCTGATGGCTTAAACCTGACATTAC
50 TGCACCAAGGGCGGATATCTACTACATAACGACCAACTATGGTAGCCAAAAGGAGAAGCTATGGC
TCTCTCTGAGTTGCTGGCCGACCTTTGGTCAACAAATCATGGAGAAGACTCAGGCAACTTGGCA
AAAATGGTGTATCTGTTAAAGACCTTATTGATGAGCAATGCTCAATTGTTAATCCAGAGACAAAAAC
GACCACCTCACCCGTCAGCAAGGGCA

3.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-6 / Schmitz 1/7 (serotype 4); SEQ ID NO: 176
55 GCAGTATTGACACAGGATGTCGCCCCATCAAAGGCTGCGCCTATGGTGTATCACTGCTAAAGTAA
AATCAAAAGAAGGAGATCTGAGCAGCTAACAGCTTAAATGGGAGGGATGGATAATGATAAAAGT
TGTGTTTGCACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGGGGATTGGATGAGGAC
TGGGAAACTTTGAGTTGATGAGCAGGAGCAGGAAAAGCCATCTGCTCATATGGCAGCAATTGGTAAG
60 AGCCACCAAGGGAGAAGCTTATCAACAGGCTAACAGGAGATGGTGTACAGGCTTACATGATGAGCT
CGATGACACCAAAATACGAGTCACACGGTATGCGACTTAAAGACATAAAAGATAGCTTA

GCTACTGGAGAACGCTTTAGGAATTGCCACAGAGGCCAAGTCATGTTATGGGTGTTTTGCCAACGAGC
 TCAGGATCAGCTGAACTCACTTTAAACGTCATGCCAGATGGCGCTTAAAGGAGCATGTGATCAA
 CCTGACTCTGGAACGCCCTAATGGCCACAGCTTAGGGCACAGCTPAATGGAAGCAATTGAAAAGCT
 AAAAAGCCGGTATCATGTTGAGCAGCAGGAATGAGCCGCTATGGATCTGACCATGATGATCCAT
 5 5 TGCCAAACAACTCAGACTATGGTTGGCGTTCTCCCTAACAGGTCGACACCAACATCAGGGCAGCTAT
 AACAGTAAGGGTATTCAACGCTTAATGACGCCAAAATAGAAAACCGTGGCGATTAAACCATGGT
 AAAGCCATTCAGAGTGTGCGActttaaaagacataaaagatgccta

> Spy0416A-6 / Schmitz 1/39 (serotype 12); SEQ ID NO: 177
 10 GCAGTATTGACACAGGGATCAGTCGCCCATCAAAGCATGCCATCAGTGATGATCAACTGCTAAAGTAA
 AATCAAAGAACAGATCTGACGCCAAAAGGCCGGTATTAATTATGGGATTGGATAATGATAAAAGT
 TGTTTGTGACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGAGGAC
 15 TGGGAAACCTTGGAGTTGAGCAGCAGGCCAAGCTTGGAGGCTTCTGGATGCTGGCTTCAACGAGC
 AACCCAGGACCGAACAAACTGTATCAAACAGAAAGAACAGATGTTACATGATAATTGACTGGACACA
 AACAGACGTGACACAAATACGAGTCACCGGTATGCGATGACAGGTATGTTAGCGGTATAGCAAAGA
 GCGCGCTACTGGAGAACGCTTTAGGGATTGACGCCAACAGGCGCTATGGATGCTGGTTTGGCA
 ACCAGCTATGGGATCAGCTGAATCTTTATCAAAGCTATGCCAGATGGCGCTTAAAGGAGCATGT
 20 GATCAACTGAGTCTGGAACCCGTAATGGGGCACAGCTTAGTGCGACGCCCTCTAATGGAAGCAATTGAA
 AAAGCTAAAAGGGCGGTATCATGTTGAGCAGCAGAAAATGAGCCGCTATGGATCTGACCATGATG
 ATCCATTGGCAAAATCAGACTATGGTTGGCTTCTCCCTAACAGGTCGACACCAACATCAGTGC
 AGCTATAAAAGCTAAGGGTATTCAACGCTTAATGACGCCAAAGAAAATAGAAAACCGTGGCGATTAAAC
 CATGGTAAGCCATTCAGAGTGTGCGActttaaaagacataaaagatAGCCTA

> Spy0416A-6 / Schmitz 1/55 (serotype 118); SEQ ID NO: 178
 25 GCAGTATTGACACAGGGATCAGTCGCCCATCAAAGCATGCCATCAGTGATGATCAACTGCTAAAGTAA
 AATCAAAGAACAGATCTGACGCCAAAAGGCCGGTATTAATTATGGGATTGGATAATGATAAAAGT
 TGTTTGTGACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGATGAGGAC
 TGGGAAACCTTGGAGTTGAGCAGCAGGCCAAGCTTGGAGGCTTCTGGATGCTGGCGCTTAAAGGAGCATGT
 30 CAACCCAGGACCGAACAAACTGTATCAAACAGAAAGAACAGATGTTACATGATAATTGACTGGACACA
 AACAGACGTGACACAAATACGAGTCACCGGTATGCCATGACAGGTATGGCTATGAGCTGGCGATAGA
 GCGCGCTACTGGAGAACGCTTTAGGGATTGACGCCAACAGGCGCTAACAGTATGTTGACTGGTITTTGCA
 ACGAGCTATGGGATCAGCTGAATCACTTTATCAAAGCTATGCCAGATGGCGCTGGCTTAGGGAGCATGT
 35 GATCAACTGAGTCTGGAACCCGCTATGGGAGCAGCTTAGTGCGACGCCAACGCTCTAATGGAAGCAATTGAA
 AAAGCTAAAAGGGCGGTATCATGTTGAGCAGCAGAAAATGAGCCGCTATGGATCTGACCATGATG
 ATCCATTGGGACAATCAGACTATGGTTGGCTTCTCCCTAACAGGTCGACACCAACATCAGTGC
 AGCTATAAAAGCTAAGGGTATTGAGCAGCTTAACGCTTAATGACGCCAAAGAAAATGGAAAACCGTGGCGATTAAAC
 CATGGTAAGCCATTCAGAGTGTGCGACTTAAAGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/56 (serotype 28); SEQ ID NO: 179
 40 GCAGTATTGACACAGGGATCAGTCGCCCATCAAAGCATGCCATCAGTGATGATCAACTGCTAAAGTAA
 AATCAAAGAACAGATCTGACGCCAAAAGGCCGGTATTAATTATGGGAGTTGGATAATGATAAAAGT
 TGTTTGTGACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGATGAGGAC
 TGGGAAACCTTGGAGTTGAGCAGCAGGCCAAGCTTGGAGGCTTCTGGATGCTGGCGCTTAAAGGAGCATGT
 45 CGATGACACAAATACGAGTCACCGGTATGCGATGAGGTATGGCTACATGTTAGTGAGGGTAAATGAAAGGCGCT
 GCTACTGGAGAACGCTTTAGGGATTGACGCCAGAGGCCAACAGTCATGTTATGGCTTCTGGCAACGAGC
 TCTGAGTCTGGGACCCCTAATGGTGCACGCCAGCTTAGTGCGACGCCAACGCTCTAATGGAAGCAATTGAAAAGCT
 CCGTACTGGGACCCCTAATGGTGCACGCCAGCTTAGTGCGACGCCAACGCTCTAATGGAAGCAATTGAAAAGCT
 50 AAAAAAGCCGGTGTATCATGTTGAGCAGCAGAAAATGAGCCGCTATGGATCTGACCATGATGATCCAT
 TGCCAAACAAATCAGAGCTATGGTTGGCTTCTCCCTAACAGGTCGACACCAACATCAGTGGCGCTAT
 AAACAGTAAGGGTATTCAACGCTTAATGACGCCAAAGAAAATGGAAAACCGTGGCGATTAAACCATGCT
 AAAGCCATCTTCAGAGTGTGCGACTTAAAGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/94 (serotype 1); SEQ ID NO: 180
 55 GCAGTATTGACACAGGGATCAGTCGCCCATCAAAGCATGCCATCAGTGATGATCAACTGCTAAAGTAA
 AATCAAAGAACAGATCTGACGCCAAAAGGCCGGTATTAATTATGGGAGTTGGATAATGATAAAAGT
 TGTTTGTGACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGATGAGGAC
 TGGGAAACCTTGGAGTTGAGCAGCAGGCCAACGCTCAAACAGACATGCTGGCTTAAAGGAGCATGT
 60 CAACCCAGGACCGAACAAACTGTATCAAACAGAAAGAACAGATGTTACATGATAATTGACTGGACACA
 AACAGACGTGACACAAATACGAGTCACCGGTATGCGATGAGGTAAATGCAAGAA

GCCTGCTACTGGAGAACGCCCTTTAGGAATTGACCCAGGGCCAAGTCATGTCATGGGTGTTTGGCA
 ACGACATCATGGGATCAGCTGAATCACTTTATCAAAGCTATCGAAGATGCCGTGGTTAGGGCAGATGT
 GATCACCTGAGCTTGGAACCCCTAAAGGGCACAGCTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 AAAGCTAAAAGAACCCGGTGTAGTGTGAGCAGGAAATGAGCGCTATGGATCTGACCATGATG
 5 ATCCATTGGCAGAACATTCAGACTATGGTGGCTTCCCTCAACAGGTGCAACACCAACATCATGTC
 AGCTATAAACAGTAAGGGTGTAGTCAACGCTAAAGGAGTAAAGACATAAAGATAGCCTA
 CATGGTAAAGCCATCTTACAGACTGTGCGACTtAAAGACATAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/253 (serotype 49); SEQ ID NO: 181
 10 GCAGTTATTGACACAGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
 AATCAAAAGAACAGACATGCTAGCACGCCAAAAGGCCGGTATTAAATTAGGGAGTTGGATAATGATAAAGT
 TGTTTGGCACATAATTATGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGTTTGATGAGGAC
 15 TGGGAAAACCTTGGAGTGTAGTGTAGCAGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 AACACAGCTAGTACAGGCAACAGCTTAGTGTAGCAGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCA
 GCCGCTGCTACTGGAGAACGCTTTAGGAATTGACCCAGGGCCAAAGTGTAGCAGGTTGATGCCCTTGGCA
 ACAGCTCATGGGATCAGCTGAATCACTTTATCAAAGCTATCGAAGATGCCGTGGTTAGGGCAGATGT
 GATCACCTGAGCTTGGAACCCGCTAATGGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 20 AAAGCTAAAAGCCGGTGTAGTGTAGCAGGAAATGAGCGCTTATGGATCTGACCATGATG
 ATCCATTGGCAACAAATCCAGACTATGGTGGCTTCCCTCAACAGGTGCAACACCAACATCATGTC
 AGCTATAAACAGTAAGGGTGTAGTCAACGCTAAATGAGGTTAGAAAACCGTGGCGATTAAAC
 CATGGTAAAGCCATCTTACAGACTGTGCGACTTAAAGACATAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/174 (serotype 6); SEQ ID NO: 182
 25 GCAGTTATTGACACAGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
 AATCAAAAGAACAGACATGCTAGCACGCCAAAAGGCCGGTATTAAATTAGGGAGTTGGATAATGATAAAGT
 TGTTTGGCACATAATTATGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGATGAGGAC
 TGGGAAAACCTTGGAGTGTAGTGTAGCAGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 CAACCCAGGACCGAAGAAAAGTGTATCAAACAGAGAAAACAGATGGTTCACATGATAATTGACTGGACACA
 30 AACACAGCTAGCAGAACAAATACAGCTACAGGCTATGAGCTAGTGTAGCAGGTTAGTGGCGTAATGAAAGAA
 GCCGCTGCTACTGGAGAACGCTTTAGGAATTGCCAGAGGGCCAAAGTGTAGCAGGTTGATGCCCTTGGCA
 ACAGCTCATGGGATCAGCTGAATCACTTTATCAAAGCTATCGAAGATGCCGTGGCTTAGGGCAGATGT
 GATCACCTGAGCTTGGAACCCGCTAATGGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 AAAGCTAAAAGCCGGTGTAGTGTAGCAGGAAATGAGCGCTTATGGATCTGACCATGATG
 35 ATCCATTGGCAACAAATCCAGACTATGGTGGCTTCCCTCAACAGGTGCAACACCAACATCATGTC
 AGCTATAAACAGTAAGGGTGTAGTCAACGCTAAAGGAGTAAAGAAAACCGTGGCGATTAAAC
 CATGGTAAAGCCATCTTACAGACTGTGCGACTTAAAGACATAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/176 (serotype 83); SEQ ID NO: 183
 40 GCAGTTATTGACACAGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
 AATCAAAAGAACAGACATGCTAGCACGCCAAAAGGCCGGTATTAAATTAGGGAGTTGGATAATGATAAAGT
 TGTTTGGCACATAATTATGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGATGAGGAC
 TGGGAAAACCTTGGAGTGTAGTGTAGCAGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 CAACCCAGGACCGAAGAAAAGTGTATCAAACAGAGAACAGATGGTTCACATGATAATTGACTGGACACA
 45 AACACAGCTAGCAGAACAAATACAGCTACAGGCTATGAGCTAGTGTAGCAGGTTAGTGGCGTAATGAAAGAA
 GCCGCTGCTACTGGAGAACGCTTTAGGAATTGCCAGAGGGCCAAAGTGTAGCAGGTTGATGCCCTTGGCA
 ACAGCTCATGGGATCAGCTGAATCACTTTATCAAAGCTATCGAAGATGCCGTGGCTTAGGGCAGATGT
 GATCACCTGAGCTTGGCACAGCCTAATGGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 AAAGCTAAAAGCCGGTGTAGTGTAGCAGGAAATGAGCGCTTATGGATCTGACCATGATG
 50 ATCCATTGGCAACAAATCCAGACTATGGTGGCTTCCCTCAACAGGTGCAACACCAACATCATGTC
 AGCTATAAACAGTAAGGGTGTAGTCAACGCTAAAGGAGTAAAGAAAACCGTGGCGATTAAAC
 CATGGTAAAGCCATCTTACAGACTGTGCGACTTAAAGACATAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/234 (serotype 44); SEQ ID NO: 184
 55 GCAGTTATTGACACAGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
 AATCAAAAGAACAGACATGCTAGCACGCCAAAAGGCCGGTATTAAATTAGGGAGTTGGATAATGATAAAGT
 TGTTTGGCACATAATTATGAAAATAGCGATAATATCAAAGAAAATCAATTGAGGATTGGATGAGGAC
 TGGGAAAACCTTGGAGTGTAGCAGGCAACAGCTTAGTGGCACAGCCTCTAATGAAAGCAATTGAA
 CAACCCAGGACCGAAGAAAAGTGTATCAAACAGAGAACAGCTCAAAGGATCTGACCATGTC
 60 AACACAGCTAGCAGAACAAATACAGCTACAGGCTATGAGCTAGTGTAGCAGGTTAGTGGCGTAATGAAAGAA

5 GCCGCTGCTACTGGAGAACGCTTTTAGGGAATTGCACCAAGGGCAGTCATGTTCATGGTGTGTTTGCCA
 ACGGCATGTCAGGGATCAGCTGAATCACTTTATCAAGCTATCGAAGATCCGGTGGCTTGGAGCAGATGT
 GATCACACCTGAGCTCTGGAACCGCTAAATGGGGCACAGCTTAGTGGCACAGGCCCTAATGGAAAGCAATTGAA
 AAAGCTAAAGAACGGCGGTATCAGTTGTTGAGCAGCAGGAAATAGGCGGCTTATGGATCTGACCATGATG
 10 ACCACATGGCAACAAATCCAGCATATGGTTGGTCTCCCTAACAGGTCGAACACCAAATCATGTCG
 AGCTATAAACAGTAAGGGTGAATTCAACGCTTAATGACGCCAAAGAATTGGAAAACCGTGGCGATTAAAC
 CATGGTAAAGCCATCTattcAGAGTCTGTCGACTTAAAGACATAAAAGATAGCCTA

10 > Spy0416A-6 / Schmitz 1/22 (serotype 4); SEQ ID NO: 185
 11 GCAGCTTGTGACACAGGGATCAGTCAGCCGCCATCAAAGCATGGCCCTACAGTGAATGTTGATCAACTGCTAAAGTAA
 AATCAAAGAAGCATGCTAGCACGCCAAAGGCCGGCTTATTAATTATGGGAGTTGGATAATGATAAAAT
 TGTTTGACACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGGGGATTGGATGAGGAC
 AGGGAAAACCTTGGAGTTGAGCAGCAGGAAACAGGCTTACAAAAAAACAAGATCTATGCTCCCAATCAACCC
 15 CGATGACACAAATACGAGTCACCGTATGTCAGCTAGGTTACATGTTAATTCAGTGGACACAAACAGA
 AGGCACCGAAGAACAGTATCAAACAGAAAGAACAGATGTTGACATGTTAATTCAGTGGACACAAACAGA
 GCTACTGGAGAACGCTTCTTGGAAATTGACGCCAGGGCCCAAGTCTAGTTGCTATGGCAACAGC
 TCATGGGATCAGCTGAATCACTTTATCAACAGCTATCGAAGATGCCGCTTCTTGGAGCAGATGTTGATCAA
 CTTGAGTCTGGAACGCTTAATGGGCCACGCTTATGGCAGCAGGCCCTAATGGAAAGCAATTGAAAAGCT
 20 AAAAGAACGGCGTATCAGTTGTTGAGCAGCAGGAAATAGGCCGCTATGGATCTGACCATGATGATCCAT
 TGGCAACAAATCAGACATGTTGCTGCTTCTCTAACAGGTCGAACACCAAATCATGTCGACCTAT
 AACAGTAAGGGTGAATTCAACGCTTAATGACGCCAAAGAATTAGAAAACCGTGGCGATTAAACCATG
 AAAGCCATCTATTCAAGAGTCTGTCGACTTAAAGACATAAAAGATAGCCTA

3.6 Antigenic fragment Spy0416A-7

25 > Spy0416A-7 / SF370 (serotype 1); SEQ ID NO: 16
 26 TCACAAATCACTCTAACGACAAATCTGGAAAAAGAGCAACACAAGATCACAGCTAGTCTGTGAGCCAACCACAACTG
 AGCTAGCTGACACAGATGCCGATCATCAATGGCTTAATCACAGGTTCTGTCAGCTCAAAAGGGCTTCTTAC
 GCCAGCTAACACAGATGTTCACGATTGGTAAAACCAAAAGGAGCTTGGGACAAGGGATAACAAAGGACAAGGC
 30 AAAGGTGTCGCGATTGATCACAGGGATCGATCCGGGCCATCAAAGCATGCCGATCAGTGAATGTTAATCACT
 CTTAAAGTAAATCAAAAGAACAGATCTGACAGGCCAAAAGGCCGGCTTAAATTATGGGAGTTGGATAAA
 TGATAAAGTTGTTTGCACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATT
 GTGAGGACTGGAAAACCTTGGTTGATGTCAGGCCAGGACAGGCAAAAGGCCATCAAACAGATCTAC
 35 GTCCCCCATCAACAGGCCAGGCCAAAAGAACAGATGTTCACATGTTAACAGTGTGATTTGA
 CTGGACACAAACAGACGATGACACCAAATACGAGTCACCGGTATGATGTCAGCAGGTATTGTTAGCCGTAAT
 ACGCAAGGGCCTGCTACTGGAGAACGCTTCTTGGAGATTGTCAGGCCAGGGCCCAAGTCTAGTGTCT
 TTTTGCCAACGACATCTGGGATCAGCTGAATCACTTTTAAACAGCTATCGAAGATGCCGCTTCTAG
 AGCAGATGATCAACCTGAGCTTGGGACCCGCTAATGGGCCACAGCTTAGTGGCAGCAGGCCCTAATGGAA
 40 GCAATTGAAAAGCTAAAGGGCGGTATCAGTTGTTGAGCAGCAGGAAATAGGCCGCTATGGGATCT
 ACCATGATGTCATTGGGACACAATCCAGACTTGGTTGCTGGCTTCTCTAACAGGTCGAACACAA
 ATCAGTGGCAGCTATAACAGTAAGTGGTCAAGCTTAATGCGCTAAAGGATCTGCGCTTAAAGACATA
 ATAATGCGCATCATTTGCTTATGTCAAAGAGTCACCTGAGCTGGGTTATAACGCACAGACGTTAAAGGTA
 45 AATTGCTTAAATGAAACGTTACATCCAAACCTATGCGAAATGTTGGCTAAGAACATGGGATCT
 CTGGGAGACTTATTTTAAACAAGCTGGTCAATCAAAGGCCATCAAGGCTTAACAGCTATGGGATG
 GGATACCATCTGCTTATCGCACGAATTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
 T

3.7 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

50 > Spy0416A-7 / Schmitz 1/7 (serotype 4); SEQ ID NO: 186
 51 TCACAAATCACTCCCAAGACAAATCTGGAAAAAGAGCAACACCAAGGTCTAGTCTGTGAGCCAACCACAACTG
 AGCTAGCTGACACAGATGCCGATCATCAATGGCTTAATCACAGGCTCTGTCAGCTCAAAAGGGCTTCTTAC
 GCCAGCTAACACAGATGTTCACGATTGGTAAAACCAAAAGGAGCTTGGGACAAGGGATAACAAAGGACAAGGC
 55 AAAGGTGTCGCGATTGATCACAGGGATCGATCCGGGCCATCAAAGCATGCCGATCAGTGAATGTTAATCACT
 CTTAAAGTAAATCAAAAGAACAGATCTGACGCCAAAGGCCGGTATAATTATGGGAGTTGGATAAA
 TGATAAAGTTGTTTGCACATAATTATGTTGAAAATAGCGATAATATCAAAGAAAATCAATTGGGAGTT
 GTGAGGACTGGAAAACCTTGGTTGATGTCAGGCCAGGACAGGCAAAAGGCCATCAAACAGATCTAC
 60 AATCACCCAGGCCAGGAAAGAACAGTGTATCAAAACAGAAGAACAGATGTTCACATGATGTTGACTG
 ACAAACAGACGATGACACCAAATACGAGTCACACGGTATGATGTCAGCGTATTGAGCCGTAATAGCAA

GAAGCCGCTGACTGGAAACGCCTTTAAAGATTGACCAAGGCCAAGTCATGTTCATGGCTGTTTG
 CCAACGCTCATGGGATCAGCTGAATCATTCAAGATCAGCGCTGGCTTGTAGGAGCAGA
 TGTATCACCTGAGCTTGGAACCGCTATGGGCACAGCTTAGTGGCAGCAAGCCCTAAATGAAAGCAATT
 GAAAAAGCTAAAAGCCGGTATCAGTTGTTGAGCAGGAAATGAGCCGGCTATGGATCTGAGCAT
 5 ATGATCATTGGCAACAAATCCAGACTGGTGGATTCACAGCTTAATGAGCCAAAGAATTAGAAAACCGTGCCTGATT
 GGCGCTATMAACAGTAAGTGGGATTCACAGCTTAATGAGCCAAAGAATTAGAAAACCGTGCCTGATT
 AACCATGGTAAAGCCCATATTCAAGACTGGTGGCTTGGCTGGGTTATAAGCAGCTTAAAGGATAATTGC
 CGCATCAATTGCTTATGTCaaGAGTCACACTGATGGGGTTATAAGCAGCTTAAAGGATAATTGC
 10 TTAAATGAGCTGATCCAATAAACCTATGACGAAATGATTGCTTGGCTAAGAAACATGGAGCCCTGGG
 GTACTATTTTAAACAAGCGCTGTCATCAACCGCTCAATGGCTTAACAGCTAAATGGATGGGATAC
 CATCTGCTTATATCGCAGAATTGGTAAAGCCATGTCCTAAATGGCAATGGTACAGGAAC

> Spy0416A-7 / Schmitz 1/39 (serotype 12); SEQ ID NO: 187
 TCACAAATCACTCTAACGAAACATCGGAAAGAGCAACCCAAAGGTCAGTCTGAGCCAAACACAAC
 15 AGCTAGCTGACACAGATGCAGCACCATGGCTAATACAGGTCCTGATGCCACTAAAAAGCCGTTTCTTAC
 GCCGCTCAATACAGATGGCAGATTGGTAAAGGAAACCAAGGAGCTGGGACAAGGGATAACAAAGGCAAGGC
 AAGGGTGGCGAGTATTGACACGGGATGATGCCCATCAAAGCATGCCATCAGTGATGATCAACTG
 CTAAAGTAAAATCAAAAGAGGACATGCTAGCAGCAGGAAAAGCCGGGGTATTAAATTATGGAGTTGGATAAA
 20 TGATAAGGACTGGTTTGCATAATTATGTTGAAAGGATAATTCAGGATAATTCAGGAAATTCATGGAGATT
 GATGAGGACTGGGAAAATCTTGGATGAGGAGCAGGAAAAGCCATAAAACACAGATCTATC
 GTCCCAATCAACCCGGCAGCCAGGAAAGAACCTTATGTTGAAAGGAAACAGATGGTTCACTGATATTGA
 CTGGACACAAAAGACGATGACCAACAAATCAGGTACACGGTATGAGCTGAGGTTGGCGGTTAAT
 25 ACCAGATGTCATAACCTGGACTGGGAGCAGCTGATGGTAAAGCTACTGGGAGCTTAAAGGCTATGGGATCTG
 AGCAGATGTCATAACCTGGACTGGGAGCAGCTGATGGTAAAGCTACTGGGAGCTTAAAGGCTATGGGATCTG
 GCAATTGAAAAGCTAAAAGCCGGTGTACAGTTGTTGAGCAGGAGCAGGAAATGAGCGCTATGGATCTG
 ACCATGATGTCATAACCTGGCAACAAATCAGACTGGTGTACAGCTGGGAGCTTCTCCCTCAACAGGCTAACAC
 30 ATCAGTGGCAGTAAACAGTGGGATGTCATAACCTGGGAGCTTAAAGGCTATGGGAGCTTGGGAGCTTGGGATCTG
 GATTTAAACCATGGTAAAGCCATCTaTCAGAGTCTGTCGActtaaaGACATAAAAGATGGCTTGGGATCTTATG
 ATAAATGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAGCTTAAAGGTTA
 35 AATTGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAGCTTAAAGGTTA
 AATTGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAGCTTAAAGGTTA
 AATTGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAGCTTAAAGGTTA
 AATTGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAGCTTAAAGGTTA
 40 AATTGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAGCTTAAAGGTTA
 CTAAAGTAAAATCAAAAGAGGACATGCTAGCAGCAGGAAAAGCCGGGGTATTAAATTATGGAGTTGGATAAA
 TGATAAGTGTGTTGCAATATAATGTTGAAAGGATAATTCAGGAAATTCATGGCTTGGCTAAGAAACATGGCC
 45 GATGAGGACTGGGAAAATCTTGGAGTTGATGAGGAGCAGGAAAAGCCATCAAACACAGATCTATC
 GTCCCAATCAACCCGGCAGCCAGGAAAGAACCTTGGTATCAGGCTTGGGAGCTTGGGAGCTTGGGATCTG
 CTGGACACAAAAGACGATGACCAACAAATCAGGTACACGGTATGAGCTGAGGTTGGCTTGGGAGCTTGGG
 50 ACCATGATGTCATAACCTGGACTGGGAGCAGCTGAGCTGGGAGCTTAAAGGCTATGGGAGCTTGGGAGCTTGG
 ATCAGTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGG
 GATTTAAACCATGGTAAAGCCATCTaTTCAAGGAGCTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGG
 ATAAATGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAAAGCTTAAAGGTTA
 55 AATTGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAAAGCTTAAAGGTTA
 CTGGGAGTACTTATTTTAAACAAGCTGGCAATCAACCGCTCAATGGCTTAACAGCTTAAAGGATGG
 GGATACCATCTGCTTATCGCAGAATTGGTAAAGCCATGTCCTAAATGGCAATGGTACAGGAAG
 T

> Spy0416A-7 / Schmitz 1/55 (serotype 118); SEQ ID NO: 188
 TCACAAATCACTCCAGAGCAAAATCGGAAAAAGAGCAACCCAAAGGTCAGTCTGAGCCAAACACAAC
 AGCTAGCTGACACAGATGCAGCACCATGGCTAATACAGGTCCTGATGCCACTAAAAAGCCGTTTCTTAC
 60 GCCAGCTCAATACAGATGGTACAGCTGGGAGCTTGGGACAAGGGATAACAAAGGCAAGGC
 AAGGGTGGCGAGTATTGACACGGGATGATGCCCATCAAAGCATGCCATCAGTGATGATCAACTG
 CTAAAGTAAAATCAAAAGAGGACATGCTAGCAGCAGGAAAAGCCGGGGTATTAAATTATGGAGTTGGATAAA
 TGATAAGTGTGTTGCAATATAATGTTGAAAGGATAATTCAGGAAATTCATGGCTTGGCTAAGAAACATGGCC
 AGCAAAAGAGCCGCTGCTACTGGAGAACGCTTTTAGGAATTGACAGGAGCAGGAAAAGCCATCAAACAGGTT
 AGCAAAAGAGCCGCTGCTACTGGAGAACGCTTTAGGAATTGACAGGAGCAGGAAAAGCCATCAAACAGGTT
 TTTTGGAGCTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGG
 AGCAATTGAAAAGCTAAAAGCCGGTGTACAGTTGTTGAGCAGGAGGAAATGAGCCGCTATGGATCTG
 ACCATGATGTCATAACCTGGACTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGG
 ATCAGTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGG
 GATTTAAACCATGGTAAAGCCATCTaTTCAAGGAGCTGGGAGCTTGGGAGCTTGGGAGCTTGGGAGCTTGG
 ATAAATGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAAAGCTTAAAGGTTA
 AATTGCGCATATTGCTTATGTCaaAGAGCTCAACTGAGCTGGGGTTATAACGCAACAAAGCTTAAAGGTTA
 CTGGGAGTACTTATTTTAAACAAGCTGGCAATCAACCGCTCAATGGCTTAACAGCTTAAAGGATGG
 GGATACCATCTGCTTATCGCAGAATTGGTAAAGCCATGTCCTAAATGGCAATGGTACAGGAAG
 T

> Spy0416A-7 / Schmitz 1/56 (serotype 28); SEQ ID NO: 189
 60 TCACAAATCACTCCAAAGATAATCGGAAAAAGAGCAACCCAAAGGTCAGTCTGAGCCAAACACAAC

ATAAATCGCATATTGCTTGTCAAAGAGTCAACTGTGCGGGTTAACGCCAACAGCITTAAGGTA
AATTGCTTAAATTGACGCTGCCAATAAAACCTATGCCAACGAAATGATTGCTTGGCTAAGAACATGGAGC
CTGGGACTACTTATTTTAATACAAGTCGCTCAATGGCTAACAGCTATGGGATGG
GGATACCATCTGCTTCATATCGCACGATTGGTAAGGCCATGCCAATTAAATGCCATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/174 (serotype 6); SEQ ID NO: 192
 TCACAAATCACTCCAAAGACAAATCGTAAAAAGAGCAATCACAGATCTGCTGAGCCAACCAACTG
AGCTACCTGACACAGATCGCAGCATCAAGGCTTAATACAGGCTGTGCGACTCAAAAAGGCTTCTTACC
10 GCGACTCAATCACAGATGTTGCGACTTATGACAGGGATCGATCCGGCCCATCAAAAGCATCGCAGTATCAACTG
AAGGTTGTCGCAAGGATCGATCCGGCCCATCAAAAGCATCGCAGTATGATGTTATCAACTG
CTAAAGTAAATCAAAAAGAGACATGCTAGCACGCCAAAAGGCCCGGTATTAAATTATGGGAGTTGGATAAA
TGATAAGGTTTTGCAATTATGCTGAAATAGGCTATAATCAAAAGGAAATTCATCGAGGATT
15 GATGAGGACTGGGAAAATCTTGTGATGTCAGGAGGCCAAAGGCATCAAAAACACAAAGATCTAC
GTCCTAACATCAACCCAGGCCAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCATGATATTG
CTGGACACAAACAGACGACTAACATACAGCTACCGCTGATGAGGTTATTGAGCAGGTT
AGCAGGAAAGGCCGCTACTGGAGAACGCTTATTAGGAATTGACAGGCCAAAGTCTGATCGCTG
20 TTTTGCCAAACGGCTGATGGATCAGCTGAATCAACTCTTATCAAAAGCTATCGAAGATGCCGTTCTTGG
AGCAGGATGTCATCAACCTGAGTCTGGCAACGCCATACTGGTATCTGAGTGTGAGGTT
ACCATGATGATCATTGGCAACAAATCAGACTGGTGTGCTTCTCCCTCAACAGGCCAAACACCAC
25 ATCAGIGGCAGTATAAAACAGTAAAGTGGTGATTCAACGCTTAATGACGGCAAAAGGAAATTAGAAACCGTGC
GATTAAACCATGGTAAAGGCCATCAATCAGACTCTGCTGACTTTAAAACATAAAAAGATGCCCTAGGTTATG
ATAATCGCATCAATTGCTTGTCAAAGACTGCAACTGGGTTATAACGCAACAGGCTTAAAGGTA
30 AATGGCTTATTGACGCTGCCAATTAACCCACTGGTCAATTAAACGCCCTAACATCAATGGGATGG
GAATACCATCTGCTTCATATCGCACGATTGGTAAGGCCATGCCAATTAAATGCCATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/176 (serotype 83); SEQ ID NO: 193
 TCACAAATCACTCAAGACAAATCGTAAAAAGAGCAACCAACAGGCTACTCTGAGCCAACCAACTG
AGCTACCTGACACAGATCGCAGCACCATAAGGCTTAATACAGGCTGTGCGACTCAAAAAGGCTTCTTACC
GCCGACTCAATCACAGATGTTGCAAGGTTAAAACCAAGGACTGGGCAAGGGATACAAAGGCAACGG
AAGGTTGTCGCAAGTATTGACAGGGATCGATCCGGCCCATCAAGCATCGCAGTATGATGTTATCAACTG
35 CTAAAGTAAATCAAAAAGAGACATGCTAGCACGCCAAAAGGCCCGGTATTAAATTATGGGAGTTGGATAAA
TGATAAGGTTTTGCTACATATTGCTGAAAATAGGCTATAATCAAAAGGAAATTCATCGAGGATT
GATGAGGACTGGGAAAATCTTGTGATGTCAGGAGGCCAAAGGCATCAAAAACACAAAGATCTAC
GTCCTAACATCAACCCAGGCCAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCATGATATTG
CTGGACACAAACAGACGATGACCAAAATCAGACTGACAGGTTATGAGCAGGTTATTGAGCCTGTAAT
40 AGCAAAAGGCCGCTGACTGGAGAACGCTTATTAGGAATTGACAGGCCAAAGTCTGATCGCTG
TTTTGCCCAACGACTCATGGGATCAGCTGAATCACTCTTATCAAAAGCTATCGAAGATGCCGTTCTTGG
AGCAGATGATGCAACTGGGACTCTGGGACAGCTATAAGGCCAGCTTAGTGGCAGCAAGGCTTAATGGAA
GCAATGAAAAGCTAAAAGGCCGTGATCAGTTGTTGAGCAGGCCAAATGAGCGCTGATGGATCTG
ACCATGATGATCATTGGCAACAAATCAGACTGGTGTGCTGTTCTCCCAACAGGCTGAAACCCAC
45 ATCAGTGCGAGCTATAACAGTAAAGTGGGATGTCAGCTTAATAGGCTAAACGCTGCTTAAAGGAAACCTGC
GATTAAACCATGGTAAAGGCCATTATTGAGCTGTGACTTTAAAACATAAAAAGATAGCTTAGGTTATG
ATAATCGCATCAATTGCTTATGCAAAAGCTAACGTGATGCCGTTATAAAAGCACAAGGCTTAAAGGTA
50 ATTGCTTATTGACGCTGCCAATTAACCCACTGGTCAATTAGGCCAAATGAGCTTATTGCTGAAAGGCC
CTGGGAGTACTTATTGCAACAGCTGGTCAATTAGGCCCTAACAGCTTAATGGGATGG
GGATACCATCTGCTTCATATCGCACGATTGGTAAGGCCATGCCAATTAAATGCCATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/234 (serotype 44); SEQ ID NO: 194
 TCACAAATCACTCCAAAGACAAATCGTAAAAAGAGCAATCACAGATCTGCTGAGCCAACCAACTG
AGCTACGTCGACACAGATCGCAGCATCAAGGCTTAATACAGGTTCTGATGCCACTCAAAAAGGCTTCTTACC
GCCGACTCAATCACAGATGTCAGGTTGGTAAAACCAAGGACTGGGCAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAAGTATTGACAGGGATCGATCCGGCCCATCAAGCATCGCAGTATGATGTTATCAACTG
CTAAAGTAAATCAAAAAGAGACATGCTAGCACGCCAAAAGGCCCGGTATTAAATTATGGGAGTTGGATAAA
TGATAAGGTTTTGCTACATATTGCTGAAAATAGGCTATAATCAAGMNAATCAATTGAGGTT
60 GATGAGGACTGGGAAAATCTTGTGAGTGCAGATGCGAGGCCAAAGGCATCAAAAACACAAAGATCTATC

GTCCCCAATCAACCCAGGCACGGAAAGAAACTTATCAAAAACAGAAAGAACAGATGTTTCACTGATATTGA
 CTGGACACAAAAGACGATGACACCAAATACTAGCTCACACGGTATGCTGACAGGTATGTCAGCGGTAAT
 AGCAAAAGACGGCTGCTACTGGAGAACCTTTTAGAATTGCAACAGAGGCCAAGTCATGTCATGCGTG
 TTTTGGCAACGACGTATGGGATCAGCTGAATCCTTTTACAAGCTATCGGAAGATGCCGGTCTAGGTTAGG
 5 AGCAGATGTGATCAACCTAGTCTGGACCGCTATGGGCAACAGCTTAGTGGCACCAAGCCTTAATGGAA
 GCAATTGAAAAAGCTAAAAAGCCGCTGATCAGTTGTTAGCAGCAGGAAATGAGCGCTCATGGATCTG
 ACCATGATGCCATTAGGCAACAAATCCAGACTATGGTTCTGGTCTCCCTAACAGGGCAACCAAC
 ATCAGTGGCAGTATAAACAGTAAGTGGGTGATCAACGCTTAATGAGCTCAAAAGATTGGAAACCCG
 GATTAAACCATGTAAGGCATCTaTTCAAGTCTGTCGACTTAAAGACATAAAAGATAGCCTAGGTTATG
 10 ATAAATCAGCTAATTTGCTTATGCTAAAGACTGACTGCGGTTATAAAGCCAAGACGTTAAAGATG
 AATTGCTTAAATGGACTGATCCAAATAAACCTATGCAAAATGATTGCTTGGCTAAGAAACATGGCC
 CTGGGGTACTTATTTTAATAACACCCTGGTCAATCAACCCGCTAATGGCTTAACAGCTAATGGGATGG
 GGATACCATGCTTCTATCGCACGAATTGGTAAGGCCATGTCCTAAATAATGCAATGGTACAGGAAG
 T
 15 > Spy0416A-7 / Schmitz 1/22 (serotype 4); SEQ ID NO: 195
 TCACAAATCACTCCAAAGACAAATCGAAAAAGACCAACCCAAAGGCTAGTCTGAGCCAAACCAACTG
 AGCTGACTGACAGACAGTCAGCTCAATCGCTAACAGCTGCTGAGCCTAACAAAAGCCGTTTAC
 20 GCGACTAACATACAGATGTTGGCAGATTCAGGCTAACAGGACTTGGGACAGGGATAACAGGACAAGGC
 AAGGTTGCTGCACTTATGACACAGGGATCGATCGGCCCATCAAAGCATGCCATCAGTGATGTTAAC
 CTAAAGTAAATCAAAGAAGACATGCTGACAGCCAAAAGGCGCCGGTTAAATTATGGGAGTTGATAAA
 TGATAAGTTGTTTGGCACATAATTATGTTGGAAAATAGCCATAATTCANNGAAATTCATGGGGATT
 25 GATGAGGACTGGGAAAACCTTGGATGAGGCTTGGGAGACCCATCAAACAGATCTATCGTCCC
 AACATACCCAGGACCCGAAAGAAACTGTATCAACAGGAAAGACAGGACTTGGGAGTTGACTGAC
 30 ACAAAACAGCATGACCAAAATCAGCTAACACGGTATGCTGAGCTAACAGGTTAGTGGCTAGG
 GAAGCCGCTACTGGAGAACCTTTAGGAATTGCAACAGAGGCCAAGTCATGTTCATGCTGTTTG
 CCAACAGCTATGGGAGCTGTAATCCTTATCAAAAGCTATGCAAGATGCCGGCTTGGAGCAGA
 35 TGTCATCACCTGAGCTTGGCAACCCGCTATGGGCAACAGCTTAGTGGCAGCACCTCTAA
 GAAAGCTAAAAAGCCGTTGATCAGTTGGTAGCAGCAGGAAATGAGCCGCTATGGATCTGACCATG
 ATGAGCTATGGCAACAAATCCAGACTATGGTTGGCTCTCTCACAGGTGCAACACCAACATCAGT
 GGCAGCTAAACAGTAAGTGGGTGATCAACGCTTAATGAGCCAAAGATAGGAAACCCGCTGGATT
 40 AACCAGGGTAAAGCCACTTACAGACTCTGCACTTAAAGACATAAAAGATAGCTTAGGTTATGATAAT
 CGCCTAAATTTGCTTATGCAAAAGACTGACTGATGCCGGTTAAAGCACAAGACGTTAAAGATAAAT
 TTAAATGACGTGATCCAAATAACCTATGCAAAATGATTGCTTGGCTAAGAAACATGGAGCCCTGGG
 45 GTACTTATTTTAATAACAGCCTGGTCAATCAACCCGCTAATGGCTTAACAGCTAATGGGATGGGATAC
 CATCTGCTTCTATCGCACGAATTGGTAAGGCCATGTCCTAAATAATGCAATGGTACAGGAAGT

4. Spy0872

40 4.1 Full length Spy0872

> Spy0872 / SF370 (serotype 1); SEQ ID NO: 196
 GATCAAGTTGATGTCATTCCTGGCGCTCAATGATTTCACGGCGCTCTGATAATACCGGAACAGCTTACA
 45 CACCAAGTGTAAAATACCAAAATCTGGACGGCTGCTCAATTAGGTGCTTATATGGATGACGCTGAGATAGA
 CTTCAGCAAGAACATACAGGCCAACAACTATGCTGTTAGGGATATGGTGGAGCCAGTCTGCT
 AACTCTGCACTTTACAGATGAGCTCTGCTAAAGCTTAAACAAAATGAAATTGTAATGTCACCTCTG
 50 GTAAATCATGATTTGGCAGGAAGACTGATGTAATTAAACCTGATGACAGGTCAAGGGCTGATCTGAATC
 AACAAATTATGATATCACAACAAATGAGCAGCACGCTTCGATCAAACCCATGCTATGCTTATGTT
 GATAAAAAAAACCAAGGATATCCCTATGTTGGAAAACCTTATGCTTAAAGACATAGCCATTATGACAAAAA
 TCTCTTAAGATGGCTTCTGTTGACTACAGAGTTCCAAATCTCTTTAAAGCAAAATCTGCT
 55 CTATCAATTGGATGATGCTGCAACAGGAAATGGCTATGCTGAGGATATGGTGTGATGAGATGG
 AAAAAGTGAACCAAATCTGCAACAGGAAATGGCTATGCTTAAAGGAGCTTGGAGCTGTTATGG
 TGGAACTATGGCTAAAACAGCTATGCTGCAACCCCTCTCAAGGAAAAGCTTATGAGATGCTGTTAGC
 60 CTAGATGACTGATACCAAACTGTTTAAACCTCATGCAACAGGTTGGTGTGCTGAGCTGCTTAC
 CAGAAAATTGAGATATGAACTATAATGATGCTTAAATGCTTAAAGCTTAAAGCAAAATCTGCT
 CGGAACCTGCAACTAATCTCAACTATTCTAAAAGAGAAAATATTGATAAAGAATCTCTGCTGCT
 GCACAAACGCTCAGCTTACTATGCTGAAGAAAACCTTCCAACTGTTGACTTGTATGACCAATAATGGT
 GTATGGCAAGTGGCTATGCTTAAAGGAGCCATCATCTGGGAGCTGCTCACAGGCTGTCACAGG
 65 TGGTAATATCCTCAACTTCAAGTCAATGACTGGTCAACACATTACGATGTCCTAAATCAGCAATACGATGAA

AACCAGACCTATTTCTCAAATGTCAGGTTAACATACACTTATACAGATAATGATCCTAAAGAACTCTGATA
 CCCCCTCAAGGATAGTTAAGGTTATAAACAGAACATGGTAAGGAATTAACTTAAACAATCTACACCGTGT
 TGTCAACGACTTCTTATGGTGTGCTGCTTCAAGCTTAAAAAAGCTTAAATTAATCGGAGCTATT
 AACACAGATACTGAAGCTTTCATCACATAATCATACAAATTAGAGCATCAGGTTAAACTGTTAATGCTACTA
 5 TAAAAGGGTTAAAATATGTAACCTTCAACACCTTGAAGCTGCACAAAAGCTTAAATGCTGTGAAACAG
 TATCATTAGTAAGGTTTAGAATCTGTGATGCCAATCACGTCTAGTGACTTCAAGCTTAAACAG
 TCTACTGAAACACTAATAACAGCCTGGCAAAAAGAACAAACAACAAAATACTATCTCTAGTTCCA
 CTCTCCAAATAACA

10 4.2 Antigenic fragment Spy0872-2

> Spy0872-2 / SF370 (serotype 1); SEQ ID NO: 17
 GCTATAATAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
 CAACATTCTTAAACAGAAAATATTGATAAAGAACATCTCTGCGTAACTTACCAACAGGCTCAGCTTAC
 15 TATTGCTAAGAAAACCTTCCACTGTTGACTTGTCTATGCCAATATGCTGTTAATCGAAGTGACCTAGTT
 GTCAAAGGAACTGGCGGACCATCCTGGGAGCTGCACAGGCTGACAAACATTGGTAAATCTCTCAAGTCA
 TTCAAAATGACTGTCACACATTACCATGCTTAACTGACAATCACGATAAAACAGACCTTCTTCTCA
 AATGTCAGGTTAACATACACTTATACAGATAATGATCTAAAGAACTCTGATACCCCCCTCAAGATAGTTAA
 20 GTTTATAAGAACATGTTGAAGAAAATTAACCTAACACTTACACCGTTGTTGTCACAGCTTCTTATG
 GTGGTGTGATGCCATTTCAGCTTAAAAGCTTAAATATCGGAGCTTAAACAGATACTGAAGCTTT
 CATCACATATACACAAATTAGAGCATCAGGTTAAACTGTTAATGCTACTATAAAAGGGTTAAAATATTCA
 25 GTAACTTCAACCTTGAAGGTTGACAAAAGTTAGCTGTTAATAGTGTGTTAACACAGTATCATTAGTTTTA
 GAATCTGTGATGCCAATCACGTGCTAGTGAACTTCAAGCTTACGACCTTTGACTTCACTGAAAACACTAATAA
 CAGCCTGGCAAAAAGAACAAACAACAAAATACTATCTCTAGTTCACTCTCCAATAACA

25 4.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0872-2 / Schmitz 1/7 (serotype 4); SEQ ID NO: 197
 GCTATAATAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
 30 CAACATTCTTAAACAGAAAATATTGATAAAGAACATCTCTGCGTAACTTACTGAACACGGCTCAGCTTAC
 TATTGCTAAGAAAACCTTCCACTGTTGACTTGTCTATGCCAATATGCTGTTAATCGAAGTGACCTAGTT
 GTCAAAGGAACTGGCGGACCATCACCTGGGAGCTGCACAGGCTGACAAACATTGGTAAATCTCTCAAGTCA
 TTCAAAATGACTGTCACACATTACAGTGTCTTCAAACTGACAATACAGTGAAGAAAACAGACCTTCTTCTCA
 35 AATGTCAGGTTAACATACACTTACAGATAATGATCTAAGAACATCTGATACCCCCCTCAAGATAGTTAA
 GTTTATAAGAACATGTTGAAGAAAATTAACCTAACACTTACACCGTTGTTGTCACAGCTTCTTATG
 GTGGTGTGATGCCATTTCAGCTTAAAAGCTTAAATACCGGAGCTTAAACAGATACTGAAGCTTT
 CATCACATATACACAAATTAGAGCATCAGGTTAAACTGTTAATGCTACTATAAAAGGGTTAAAATATT
 40 GTAACTTCAACCTTGAAGGTTGACAAAAGTTAGCTGTTAATAGTGTGTTAACACAGTATCATTCTAGTTAAG
 TAATACAGCTTGGCAAAAAGAGATAAACACAAACAAAATACTCTCTAACAA

> Spy0872-2 / Schmitz 1/39 (serotype 12); SEQ ID NO: 198
 GCTATAATAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
 CAACATTCTTAAACAGAAAATATTGATAAAGAACATCTCTGCGTAACTTACTGAACACGGCTCAGCTTAC
 45 TATTGCTAAGAAAACCTTCCACTGTTGACTTGTCTATGCCAATATGCTGTTAATCGAAGTGACCTAGTT
 GTCAAAGGAACTGGCGGACCATCACCTGGGAGCTGCACAGGCTGACAAACATTGGTAAATCTCTCAAGTCA
 TTCAAAATGACTGTCACACATTACAGTGTCTTCAAACTGACAATACAGTGAAGAAAACAGACCTTCTTCTCA
 AATGTCAGGTTAACATACACTTACAGATAATGATCTAAGAACATCTGATACCCCCCTCAAGATAGTTAA
 GTTTATAAGAACATGTTGAAGAAAATTAACCTAACACTTACACCGTTGTTGTCACAGCTTCTTATG
 50 GTGGTGTGATGCCATTTCAGCTTAAAAGCTTAAATACCGGAGCTTAAACAGATACTGAAGCTTT
 CATCACATATACACAAATTAGAGCATCAGGTTAAACTGTTAATGCTACTATAAAAGGGTTAAAATATT
 GTAACTTCAACCTTGAAGGCTGACAAAAGTTAGCTGTTAACACAGTATCATTAGTTAAGGTTTTA
 GAAACTGTTGACAAAAGTTAGCTGTTAACACAGTATCATTAGTTGACTTCACTGAAAACACTAATAA
 CAGCCTGGCAAAAAGAACACAAACAAAATACTCTCTAACAA

> Spy0872-2 / Schmitz 1/55 (serotype 118); SEQ ID NO: 199
 GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
 CAACATTCTTAAACAGAAAATATTGATAAAGAACATCTCTGCGTAACTTACTGAACACGGCTCAGCTTAC
 55 TATTGCTAAGAAAACCTTCCACTGTTGACTTGTCTATGCCAATATGCTGTTAATCGGAGCTTAAACAGATACTGAAGCTT
 GTCAAAGGAACTGGCGGACCATCACCTGGGAGCTGCACAGGCTGACAAACATTGGTAAATCTCTCAAGTCA

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- TTCAAATGACTGGTCAACACATTACGATGCTTAATCAGCAATACGATGAAACAGAACCTATTCTCA
AATGTCAGGTTAACATACACTTACAGATAATGCTCAAGAACACTGTATATCCCTTCAAGATAGTTAAG
GTTATAAGACAAATGGTGAAGAAAATTAACTTAAACACTTACACCGTGTGTCACGACTTCTTTATG
GTGGTGTGATGCCATTACAGCTTTAACAAAAGCTAAATTAACTACAGGACTTAAACAGATCTGAAGCTT
5 CATCACATATACAAACATTAGAGCATCAGGTAACACTGTTAACACTGACTATAAAAGGGTTAAAATTAT
GTAACCTAACACCTGGAAAGTTCGACAAAAGTTAACAGTAAATGTCGTGAAACACAGTATCATTAGTAAGGTTTA
GAATCTGTGATGCCAATAGTGCTAGTGAAGTCATTTCAGACCTTTGACTCTACTGAAACACTAAATAA
CAGCCTGGAAAAAGAACaCGACAAACAAAATACTATCTCTAGTCCACTCTCCAATAACAA
- 10 > Spy0872-2 / Schmitz 1/56 (serotype 28); SEQ ID NO: 200
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAAACAAAATCGGAACTGCAACTAATTCTT
CAACTATTCTAAAACGAAAATATTGATAAAAGAATCTCTGCGTAACTTAGCAACACGGCTCAGCTTAC
TATTGCTAAGAAAACCTTCAACTGTTGACTCTGATGCCAAATATGTTGTTATTGCAAGTGCAGCTTGT
15 GTCAAAATGACGGGACCATCACCTGGGAGCTGCACAGGCTGTACAACATTGGTAAATCTTCAGTCAAGTCA
TTCAAATGACTGGTCAACACATTACGATGCTTAATCAGCAATACGATGAAAACAGACCTATTCTTCTCA
AAATGTCAGGTTAACATACACTTACAGATAATGCTCAAGAACACTGTTAACACAGATCTGAAGCTT
GTTATAAGACAAATGGTGAAGAAAATTAACTTAAACACTTACACCGTGTGTCACGACTTCTTTATG
GTGGTGTGATGCCATTACAGCTTTAACAAAAGCTAAATTAACTGGAGCTTAAACAGATCTGAAGCTT
20 CATCACATATACAAACATTAGAGCATCAGGTAACACTGTTAACAGTAAATGTCGTGAAACACAGTATCATTAGTAAGGTTTA
GAATCTGTGATGCCAATAGTGCTAGTGAAGTCATTTCAGACCTTTGACTCTACTGAAACACTAAATAA
CAGCCTGGAAAAAGAACACAAACAAAATACTATCTCTAGTCCACTCTCCAATAACAA
- > Spy0872-2 / Schmitz 1/94 (serotype 1); SEQ ID NO: 201
25 GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAAACAAAATCGGAACTGCAACTAATTCTT
CAACTATTCTAAAACGAAAATATTGATAAAAGAATCTCTGCGTAACTTAGCAACACGGCTCAGCTTAC
TATTGCTAAGAAAACCTTCAACTGTTGACTCTGATGCCAAATATGTTGTTATTGCAAGTGCAGCTTGT
GTCAAAATGACGGGACCATCACCTGGGAGCTGCACAGGCTGTACAACATTGGTAAATCTTCAGTCAAGTCA
TTCAAATGACTGGTCAACACATTACGATGCTTAATCAGCAATACGATGAAAACAGACCTATTCTTCTCA
30 AAATGTCAGGTTAACATACACTTACAGATAATGATCTGAAGAACACTGTATACCCCTTCAAGATAGTTAAG
GTTATAAGACAAATGGTGAAGAAAATTAACTTAAACACTTACACCGTGTGTCACGACTTCTTTATG
GTGGTGTGATGCCATTACAGCTTTAACAAAAGCTAAATTAACTGGAGCTTAAACAGATCTGAAGCTT
CATCACATATACAAACATTAGAGCATCAGGTAACACTGTTAACAGATCTGAAGCTTAAACAGGTTAAAATTAT
GTAACCTAACACCTGGAAAGTTCGACAAAAGTTAACAGTGTGTCACACAGTATCATTAGTAAGGTTTA
35 GAAATCTGTGATGCCAATACAGTGCTAGTGAAGTCATTTCAGACCTTTGACTCTACTGAAACACTAAATAA
CAGCCTGGAAAAAGAACACAAACAAAATACTATCTCTAGTCCACTCTCCAATAACAA
- > Spy0872-2 / Schmitz 1/253 (serotype 1); SEQ ID NO: 202
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAAACAAAATCGGAACTGCAACTAATTCTT
40 CAACTATTCTAAAACGAAAATATTGATAAAAGAATCTCTGCGTAACTTAGCAACACAGCTCAGCTTAC
TATTGCTAAGAAAACCTTCAACTGTTGACTCTGATGCCAAATATGTTGTTATTGCAAGTGCAGCTTGT
GTCAAAATGACGGGACCATCACCTGGGAGCTGCACAGGCTGTACAACATTGGTAAATCTTCAGTCAAGTCA
TTCAAATGACTGGTCAACACATTACGATGCTTAATCAGCAATACGATGAAAACAGACCTATTCTTCTCA
AAATGTCAGGTTAACATACACTTACAGATAATGATCTGAAGAACACTGTATACCCCTTCAAGATAGTTAAG
45 GTTTATAAGACAAATGGTGAAGAAAATTAACTTAAACACTTACACACTTACACCGTGTGTCACGACTTCTTTATG
GTGGTGTGATGCCATTACAGCTTTAACAAAAGCTAAATTAACTGGAGCTTAAACAGATCTGAAGCTT
CATCACATATACAAACATTAGAGCATCAGGTAACACTGTTAACAGATCTGAAGCTTAAACAGGTTAAAATTAT
GTAACCTAACACCTGGAAAGTTCGACAAAAGTTAACAGTGTGTCACACAGTATCATTAGTAAGGTTTA
50 GAAATCTGTGATGCCAATATAGTGCTAGTGAATAATTTCAGACCTTTGACTCTACTGAAACACTAAATAA
CAGCCTGGAAAAAGAACACAAACAAAATACTATCTCTAGTCCACTCTCCAATAACAA
- > Spy0872-2 / Schmitz 1/176 (serotype 83); SEQ ID NO: 203
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAAACAAAATCGGAACTGCAACTAATTCTT
CAACTATTCTAAAACGAAAATATTGATAAAAGAATCTCTGCGTAACTTAGCAACACGGCTCAGCTTAC
55 TATTGCTAAGAAAACCTTCAACTGTTGACTCTGATGCCAAATATGTTGTTATTGCAAGTGCAGCTTGT
GTCAAAATGACGGGACCATCACCTGGGAGCTGCACAGGCTGTACAACATTGGTAAATCTTCAGTCAAGTCA
TTCAAATGACTGGTCAACACATTACGATGCTTAATCAGCAATACGATGAAAACAGACCTATTCTTCTCA
AAATGTCAGGTTAACATACACTTACAGATAATGATCTGAAGAACACTGTATACCCCTTCAAGATAGTTAAG
GTTTTATAAGACAAATGGTGAAGAAAATTAACTTAAACACTTACACCGTGTGTCACGACTTCTTTATG
60 GTGGCGTGTGCTTCACTGGTTTCACTGGTAAAGCTAAATTAGTCAGGAGCTTAAACAGATCTGAAGCTT

CATCACATATATCACAAATACAACGATCAGGTAAAAGTGTAAATGCTACTATCAAAGGGTTAAAAATTAT
GTAACCTAAACCTTGAAGGATCAACAAAATTATACTGCTGGCAACACAGTATCATTAGTAGGTTTTA
GAAATCGTGATGCAATATAGTGTCTAGTAGTCAGGTTACCTTCAGCTTGCACCTACTGAAACACTAATAA
CAGCTTGGCAAAGAGACAACAAACAAAATACTATCTAATTCCACTCTTCCAATAACA

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> Spy0872-2 / Schmitz 1/177 (serotype 22); SEQ ID NO: 204
GCTATAATAAATCATGCTAATGATATTGTTAAAAGCAGTTACTGAACGAAAATCGGAACCTGCAACTAATTCTT
CAACTATTCTTCAACGAAAATATTGATAAAGATCTCTGCGTAATTCTAGTAACACGGCTCAGCTTAC
TATTGCTAAGAAAACCTTCCAACTGTTGACTTTGCTATGCCAAATAATGGTGTATTCAAGGTGACCTAGTT
10 GTCAAATGCGGCCACATCACCTGGGAGCTGCAACAGGCTGTACAACCAATTGGTAAATATCCTTCAAGTCA
TTCAATGACTGGTCAACATTACATGCTTCAAACTGAGATAATGATCTAAGAACCTCTGATACCCCTTCAAGATAGTTAAG
ATGTCAGGTTAACATACATTACAGATAATGATCTAAGAACCTCTGATACCCCTTCAAGATAGTTAAG
GTTTATAAGAACATGGTAAAGAAAATTAACTTAAGTGTCTGGTAAACACAGTATCATTAGTAGGTTTTA
15 CATCACATATATCACAAATTAGAACGATCAGGTTAAAAGTGTAAATGCTACTATAAAAGGGTTAAAATTAT
GTAACCTAAACCTTGCAGGAACTGCAACAAAAGTAAATGCTCTGGTAAACACAGTATCATTAGTAGGTTTTA
GAAATCGTGATGCAATATAGTGTCTAGTAGAAATCATTGCAACGCTTGCACCTTACTGAAACACTAATAA
CAGCTTGGCAAAGAACAcAGCAACAAAATACTATCTAGTTCACCTCTTCCAATAACA

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> Spy0872-2 / Schmitz 1/234 (serotype 44); SEQ ID NO: 205
GCTATAATAAATCATGCTAATGATATTGTTAAAAGCAGTTACTGAACGAAAATCGGAACCTGCAACTAATTCTT
CAACTATTCTTCAACGAAAATATTGATAAAGAATCTCTGCGTAATTCTAGTAACACGGCTCAGCTTAC
TATTGCTAAGAAAACCTTCCAACTGTTGACTTTGCTATGCCAAATAATGGTGTATTCAAGGTGACCTAGTT
25 GTCAAATGCGGCCACATCACCTGGGAGCTGCAACAGGCTGTACAACCAATTGGTAAATATCCTTCAAGTCA
TTCAATGACTGGTCAACATTACATGCTTCAAACTGAGATAATGATCTAAGAACCTCTGATACCCCTTCAAGATAGTTAAG
GTGGTGTGATGGCTTTGCAATTAAAAGAAAATTAACTTAACTGCGAGCTTAAACACAGTATGAGCTT
CATCACATATATCACAAATTAGAACGATCAGGTTAAAAGTGTAAATGCTACTATAAAAGGGTTAAAATTAT
30 GTAACCTAAACCTTGCAGGAACTGCAACAAAAGTAAATGCTCTGGTAAACACAGTATCATTAGTAGGTTTTA
GAAATCGTGATGCAATATAGTGTCTAGTAGAAATCATTGCAACGCTTGCACCTTACTGAAACACTAATAA
CAGCTTGGCAAAGAACAcAGCAACAAAATACTATCTAGTTCACCTCTTCCAATAACA

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> Spy0872-2 / Schmitz 1/22 (serotype 4); SEQ ID NO: 206
GCTATAATAAATCATGCTAATGATATTGTTAAAAGCAGTTACTGAACGAAAATCGGAACCTGCAACTAATTCTT
CAACTATTCTTCAACGAAAATATTGATAAAGAATCTCTGCGTAATTCTAGTAACACGGCTCAGCTTAC
TATTGCTAAGAAAACCTTCCAACTGTTGACTTTGCTATGCCAAATACTGTTGATTCAAGGTGACCTAGTT
40 GTCAAATGCGGCCACATCACCTGGGAGCTGCAACAGGCTGTACAACCAATTGGTAAATATCCTTCAAGTCA
TTCAATGACTGGTCAACATTACATGCTTCAAACTGAGATAATGATCTAAGAACCTCTGATACCCCTTCAAGATAGTTAAG
GTTTATAAGAACATGGTAAAGAAAATTAACTTAACAACTTACACAGCTTACCCGGTGTGTGCAACAGCTTCTTTATG
GTGGTGTGATGGCTTTGCAATTAAAAGGTTAAATTAACTGGAGCTTAAACACAGTATGAGCTT
45 CATCACATATATCACAAATTAGAACGATCAGGTTAAAAGTGTAAATGCTACTATAAAAGGGTTAAAATTAT
GTAACCTAAACCTTGCAGGAAAGTCAACAAAAGTAAATGCTCTGGTAAACACAGTATCATTAGTAGTAAAGG
TTTTAGAAATCGTGATGCAATATAGTGTCTAGTAGAAATCATTGCAACGCTTGCACCTTACTGAAACAC
TAATAACAGCTTGGCAAAGAGATAACACAAAATACTATCTAATTCCACTCTTCCAATAACA

5. Further Sequences

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> Spy0480 / SF370 (serotype 1); SEQ ID NO: 18
TTGGCGCAGATTCTAGTCCTTCGCTGATAGACGTTTGGAGTTGGCTTTGGAGTTGGCTATAAGGAAGAAA
CAACCTCTCAGTTTCTCGGATCAGCCCCCTCCAAGTGGTTTGATCGAGGTGAGGCTAACACGGTTAGGT
55 TGCTTATACCAACTCAGATGCTCTGATGAAAGATACTTCGATGTTGGATGGTCTGATAAGTCTTGGAC
GCTCAGATGTTCTGTTGATGGCTCATGGTTATGGGCTTCTCAACTCTGCTAGAGGGATTTTACGATGT
CAGGAGTTCTGAAAGCAGTGTCCCGTGTCACTCCATACTGAAACAAATAATAAGGTTAACTTCAAAGT
60 CATTAGGATGATCTGATACACAACTGATAAGGAACGTTTCTCTGTCACCCGAACCTTGGAAATCACC
ATGAAATCTGTTGATCAGTTACCGAGTACTGACTGACCATATTGGGTTGCTGGTATTGAAACGAATGACA
CTCTCATTAAAATCGGGGTGCCCTTAACTACAGGAGTAGTGGGGCTTCCCAAGGACAAATAATAAGTAC
TTATACTCAAAGGGGAGGCCAGGCACTTACTATGGGACGGCTACTACGGATATTATCTCCAGCAGTT
TTATGGAAAAAGGCTCCGTAAGAGGCTACTGAAGGCCATCACTGTCGGAACACCGACTCTGGTATTTC

CTGGTAAATTCACCGAGGCCAGAGCTTAACGAGCATGAAGCTATGGTAATGTCGAACCACTGTCATGT
AGTAAAAGAACATAAAGGTCATAGATTTAAACAGGCTTACACGGGCGTTGAGCCTTATAGACTAATGAAGAT
GAGAAGGGAGAACGCTGCCAGCATGTTAAGGTTAAGCACCCAGAAGTGGTAGCTGGCTAGAACAGCAG
CTCTTCTAGTGTGAATGAGCGCTGAGGCAGGTAAAAAGT

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> Spy0895 / SF370 (serotype 1); SEQ ID NO: 19
ACTAAATACAAACATAGACATCCTTTGGATGTCATGCTTATAATCAGGCCCTTAAAGATTCGTTAAAGCCT
TGCCAATATCACCCTAAAGTCGCCCTCATTTACTAGAGATTTAAAGAGGCCAGAGAATGAACTTCGCCCT
TCTAGCGGAACATGCAAGAGAACCGGACATTGAAGACAGTATCACTGTCATTATGCCCTAACCAATCG
10 CTGGAAGATGAGCAGATGCCCAATTACATTGGATTTAGAAGTAAAGTAAAGGAAACCGGTCTTATTTGAT
TCGTCAGGTCAGTGGCCCTATTCTTACCGACTTCTCAGACTATCACTGCAAGAAATTCGCCCTAACCAATCG
GGCTTATATTTGATACAAGAATGACCAATATGACACTGGCATTTCAGGCCATGTTGGAACTGATCAC
GGGGTAAAGGCTCTGGCTCAAAAGCAGTCGACAGCAGGACCAAAAGCTTAGCAGACATGTTGA
15 CTTGACCTCTTACCTCAGGAAATCAAGGACTTGGTTTTGATGACATTGAAAGGGCTGTCGCAA
TCCTCTGGCTCATTTGATTAAGCCTTTGATGAAGAGGAACGTCATCGCACCACTCATTTCTCTCAGGCT
TTTTGGAAAACATTACCTTGGCACTTTCTGCTGAATTAACCGACGTGAGCCTTTACTTTGAT
ACATGAATGCCATTAAAGGAGTTGAGCCTTGGAGAACATCTATTGTC

15

> Spy1536 / SF370 (serotype 1); SEQ ID NO: 207
20 ATGAAATGCTGGAGGCCCTACGATATTGGACTGCTTACAAAGTCATGGCAAAGAACGAAACGAAAG
GAGCTTACCAAGCTTGTGTCAGTGGCATTTAGTCGTCGCCAGCCTCGCTCAGCTTATTATGCTGGCTGACCC
GTTTACTGAAATTAGTCAGCAGAACAGAACACAGGCCGATACAGCAGTGTGATTCTCGGAAATTATC
TTTACATGAAACATCAAAATCAGCTATTATCAAGCTTATCTAGCTGGAAAACCGCTTACATTAG
ATTATAAAGGGCTATGTTTAAAGCAGTAAACGAACTACTTTAAAGGAACGCTACACTTACAGCAGATAC
25 TGTAAACGGTGTAAATGGTAAACAGTTACTAGTCAGCAACATTGACTATGTTCTCACCTAAACATCA
GGGGATGAAGTTACGGTTCAGTTACAGGTGATAATAAGCTAAAAAGGATTTGGCGTATATCAAACCTGA
AAAATGGGAAATAATGGGATTTGGCATTTCTGCTGATCATACAGTGTCAATTGAGAACACAGTATG
TTAGTACTAAAGGAGTAGGGAGGACTTAGTGGCTGGTCAATGTTTACTCTGATATATAATGATCAAATCAA
30 GAAGATTTACGCAAGGGCGTACAATTGCAAGGTCAGGAACATTGGCAAGGATGGCGAAGTAGGAGATATTG
GTGGTCAGGCTTAAAGGATTTAGTGTGACAGCTGAAGCTGAGCATATTGTTTGTGTCGAAATAATCTGT
TGATAAGGAAATAAAAGGATTTCTGATCAAATGCTAAAGTAAATTACGAAGAACGCAAACGGCGCAGCAACGA
CTAAAGACCAAAATGAAGATGTTCTGTACGACTGTTCAAGAGGACTGGTTATCTCGCAAA

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> Spy1666 / SF370 (serotype 1); SEQ ID NO: 208
35 ACAAAAGAATTTCATCACGTCAGCTTACGGTAAACAGTCGGACATGCTTGCACATAAACGCTGATGGGA
TTTATGTTGATGCGACGCTAGGGCTCAGGCCCTACGGCTTATTGTTGCAAACTTGGTGAAGAGGGCA
CCTCTATTGTTGACCAAGACCAAAAGGCTATTGACAATGCCAACCTTCAATTTATGCAAA
GGACAGTAACTTTATAAAGATAATTAGACACCTTCAAGGACAGTAAACAGCCTGGAGGTGATGAA
40 TTGATGTTATCTTATGACCTTGGCTTCCAGGCCGCAATTGGATGAAAGAGAACGAGGGTTCTTATAA
ACAAGATGCTTACCTGGATGCGCTTCAAGGCTTCAAGGCTTCAAGGCTTCAAGGCTTCAAGGCTTCA
CCATTCAATGATTGGTAAAGATTTTTCAATAATGAGAAATTTCTCAAGGCTTCAAGGCTTCAAGGCTTCA
TTGACACAGAACAGCTTAAAGGACTTATGACAAACACAGTGGCAGAATTTGATTAAGGCGAACAGGC
45 AGCTAAAGAGTTGAAGAAAAAGGCCACCCGTCAACAGATTTCAGCTTCAAGGCTTCAAGGCTTCA
GAATTGGGGAGATGTAATTCAGGAGCTTAAAGGATTTAGGCTTGTGATGGCTGATCTCAGTT
TTACCTTCATTCTGGAGATGCCCTAACCAAGCAGTTTAAAGAGCTAGTACGGTGGATGTGCCCC
AGGGCTTCTCTAATTCTGAAGATATGAAACCTAAGTTGAACTTGTTCACGTAAGCGATCTTACCTAGT
CATTCAAGTTAACAGCTAATAAAGGGCACACTCAGCCTAACAGTGTGCCCCAAAATTCGAAA

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> Spy1727 / SF370 (serotype 1); SEQ ID NO: 20
50 GTGACAACGAGGCCAACAGAACACTTACCTTGCCTTACGGCTGGGAAAGTGGCAAAGCTTATAAGGACTT
ATCCTAACATGGGAATGTGCTTTATAAAATTAAATCAGGCCCTATTCTACCTGCCCTAGAAAAGAACAGAT
TGCCCTACAGTACTTGGGCCAACGCCATGGCAATGTTGATGAGTGGCTAACAGGCTTAAACGGC
CGTACATTGACCAAGAACAGATGAAACGAACTTCACTTCAATTGCTTCAAGGCTTCAACATCTAAA
AATTAGTCATCACTGCTTCACTTAAATGAGTAAAGAACCCATACGATTATTGGTTGATTTGGCA
55 AAATGACCCCTTGCCTAACAGCTTACCTTCAAGCTTCACTTCAAGGCTTCAAGGCTTCAACATCTAAA
GAGTCAATCAGAAGTGGCAACGATTGTCATGGAGATTAACATGCAATTGGGTGATTTACTAGTG
GTATGTTTTTTAGTGGATTTGGCTTCTGCTGCTAACAGTGGATGTTGATGTTGCTTACCTGTTGAG
CCACTATTTCCACGGCTCTGTTGGTCAAGATGGCTCTTATTGCTTAAAGAATGACAAAGGTTATG
60 CAAAATTTGGTATGGTCAATTCTCACCTGACACAATTCTCAAGTGTGTTGACAAACGCTGACATGG
AGCATGTAATCAGGAGATTATGCCCTCAGAAAATTAGAGAAATATTAGAAAAGAAA

Claims

- 5 1. A peptide consisting of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3.
- 10 2. A peptide consisting of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3, and
- 15 a) 1 to 350 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 1; or
- 20 b) 1 to 200 additional amino acid residue(s), preferably 1 to 150, more preferably 1 to 100, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is SEQ ID NO: 2; or
- 25 c) 1 to 100 additional amino acid residue(s), preferably 1 to 75, more preferably 1 to 50, even more preferably at most 1 to 25, still more preferably at most 1 to 10, most preferably 1, 2, 3, 4 or 5 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 3; or
- 30 d) 1 to 150 additional amino acid residue(s), preferably 1 to 100, more preferably 1 to 75, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 4; or
- 35 e) 1 to 450 additional amino acid residue(s), preferably 1 to 300, more preferably 1 to 150, even more preferably at most 1 to 100, still more

preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 20, 30 or 40 additional amino acids residue(s) if the antigen is SEQ ID NO: 5; or

- 5 f) 1 to 250 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 6 or SEQ ID NO: 7.

10 3. The peptide of any of claims 1 or 2 further consisting of at least one amino acid residue heterologous to the antigen, preferably an additional amino acid sequence comprising a marker protein.

15 4. The peptide of any of claims 2 or 3, wherein the additional amino acid residue(s) is/are flanking the antigen C-terminally, N-terminally or C- and N-terminally.

20 5. The peptide of any of claims 1 to 4, wherein the functional active variant is essentially identical to any of the antigens of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3, but differs from the antigens of any of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3 in that it is derived from a homologous sequence of a different serotype of *S. pyogenes*, particularly wherein the serotype is M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118.

25 6. The peptide of any of claims 1 to 5, wherein the functional active variant is a portion of any of the SEQ ID NOS: 1 to 7 consisting of at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% of the amino acids of the antigen of any of the SEQ ID NOS: 1 to 7.

30 7. The peptide of any of claims 1 to 6, wherein the functional active variant of the antigen of any of the SEQ ID NOS: 1 to 7 has at least 50% sequence identity to the

antigen of any of the SEQ ID NOS: 1 to 7, especially at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% sequence identity to the antigen of any of the SEQ ID NOS: 1 to 7.

5

8. The peptide of claim 7, wherein the variant is derived from the antigen of any of the SEQ ID NOS: 1 to 7 by at least one conservative amino acid substitution.

10

9. A peptide comprising an amino acid sequence with at least 95% sequence identity to at least one of SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7, wherein said peptide is not Spy0269, Spy0292, Spy0416A, or Spy0872.

15

10. A peptide characterized in that it comprises at least 2, preferably at least 3, more preferably at least 4 antigens as defined in any of claims 1 to 9.
11. A nucleic acid coding for the peptide according to any of claims 1 to 10 or a nucleic acid complementary thereto, particularly a DNA sequence of any of the sequences of SEQ ID NOS: 11 to 17 or the corresponding RNA sequence.

20

12. The nucleic acid of claim 11, wherein the nucleic acid is located in a vector.

25

13. A pharmaceutical composition, especially a vaccine, comprising
 - (i) at least one peptide according to any of claims 1 to 10 and/or
 - (ii) at least one peptide comprising or consisting of the sequence of any of the SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, or a functional active variant thereof, and
 - (iii) optionally a pharmaceutically acceptable carrier or excipient.

30

14. A pharmaceutical composition containing
 - (i) a nucleic acid according to claim 11 and/or a nucleic acid complementary thereto and/or
 - (ii) a nucleic acid coding for the peptide comprising or consisting of the sequence of any of the SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10,

particularly a DNA sequence of any of the SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20, or a functional active variant thereof or a nucleic acid complementary thereto or the corresponding RNA sequence, and

- (iii) optionally a pharmaceutically acceptable carrier or excipient.

5

15. The pharmaceutical composition of claim 14, wherein the nucleic acid is comprised in a vector and/or a cell.

10

16. An antibody or functional active fragment thereof which binds specifically to the antigen of claim 1.

17. The antibody or functional active fragment thereof of claim 16, wherein the antibody is a monoclonal, polyclonal, chimeric or humanized antibody, or wherein the functional active fragment comprises a Fab fragment.

15

18. A hybridoma cell line which produces the antibody according to claim 16 or 17.

19. A method for producing an antibody according to claim 16 or 17, characterized by the following steps:

20

- (a) administering an effective amount of the peptide according to any of claims 1 to 10 to an animal; and
(b) isolating the antibody produced by the animal in response to the administration of step (a) from the animal.

25

20. A method for producing an antibody according to claim 16 or 17, characterized by the following steps:

30

- (a) contacting a B cell with an effective amount of the peptide according to any of claims 1 to 10;
(b) fusing the B cell of step (a) with a myeloma cell to obtain a hybridoma cell; and
(c) isolating the antibody produced by the cultivated hybridoma cell.

21. The method of claim 19 or 20, wherein the isolated antibody is additionally purified.
22. A pharmaceutical composition, especially a vaccine, comprising the antibody
5 according to claim 16 or 17.
23. A pharmaceutical composition comprising the peptide as defined in claim 13 or the nucleic acid as defined in claim 14 or the antibody or functional fragment thereof according to claim 16 or 17 for the immunization of a subject against an infection or the treatment of a subject having an infection, wherein the infection is preferably 10 a *S. pyogenes* infection.
24. Use of the peptide as defined in claim 13 or the nucleic acid as defined in claim 14 or the antibody or functional fragment thereof according to claim 16 or 17 for the manufacture of a medicament for immunization against or treatment of an infection, 15 preferably a *S. pyogenes* infection.
25. Method of immunizing a subject against an infection or treating a subject having an infection, the method comprising
20 (a) administering to the patient an effective amount of the peptide as defined in claim 13 or the nucleic acid as defined in claim 14 or the antibody or functional fragment thereof according to claim 16 or 17.
26. The method of claim 25, wherein the infection is a *S. pyogenes* infection.
25
27. A method of diagnosing a *S. pyogenes* infection comprising the steps of:
30 (a) contacting a sample obtained from a subject with the peptide according to any of claims 1 to 10; and
(b) detecting the presence of an antibody against *S. pyogenes* in the sample.
28. A method of diagnosing a *S. pyogenes* infection comprising the steps of:
35 (a) contacting a sample obtained from a subject with the antibody according to claim 16 or 17; and

- (b) detecting the presence of an antigen of *S. pyogenes* in the sample.
29. A method for identifying a ligand capable of binding to a peptide according to any of claims 1 to 10 comprising:
- 5 (a) providing a test system comprising the peptide,
- (b) contacting the test system with a test compound, and
- (c) detecting a signal generated in response to the binding of the test compound to the peptide or functional active variant.
- 10 30. Use of any of the peptide according to any of claims 1 to 10 for the isolation and/or purification and/or identification of an interaction partner of the peptide.

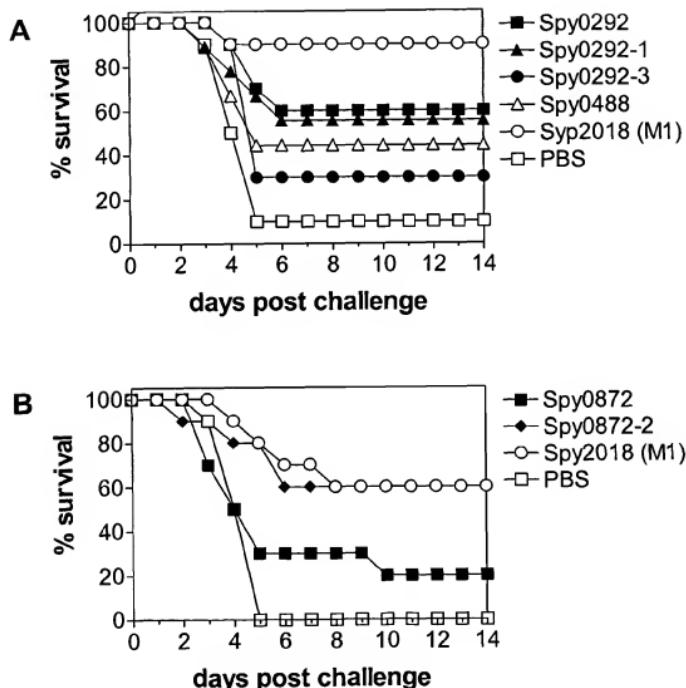
Figure 1**CFA/IFA model**

Figure 2

CFA/IFA model

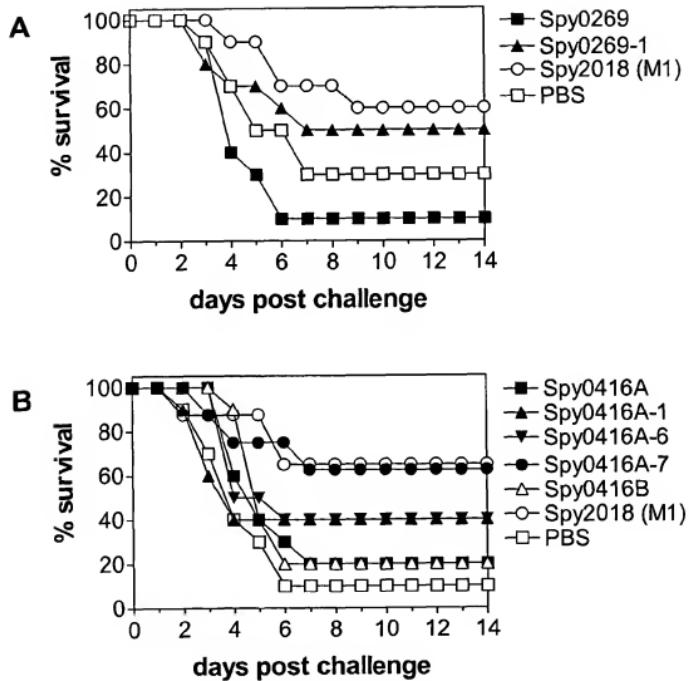


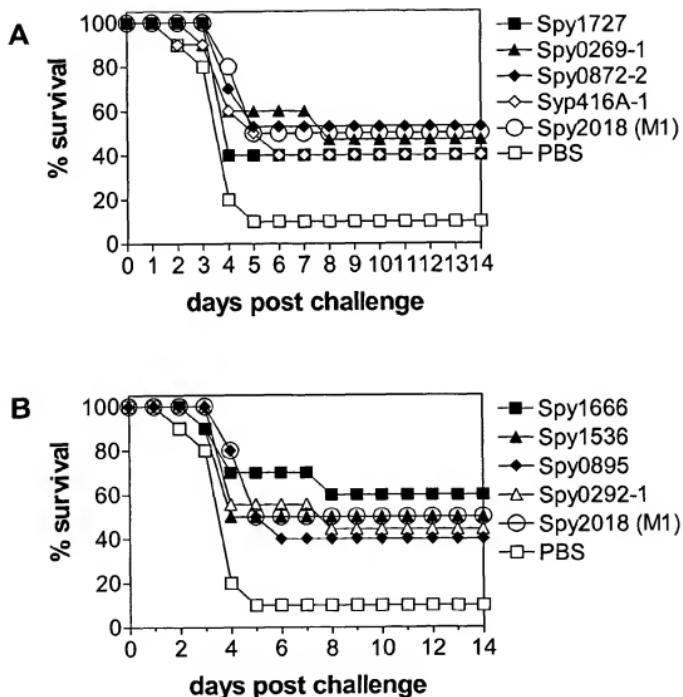
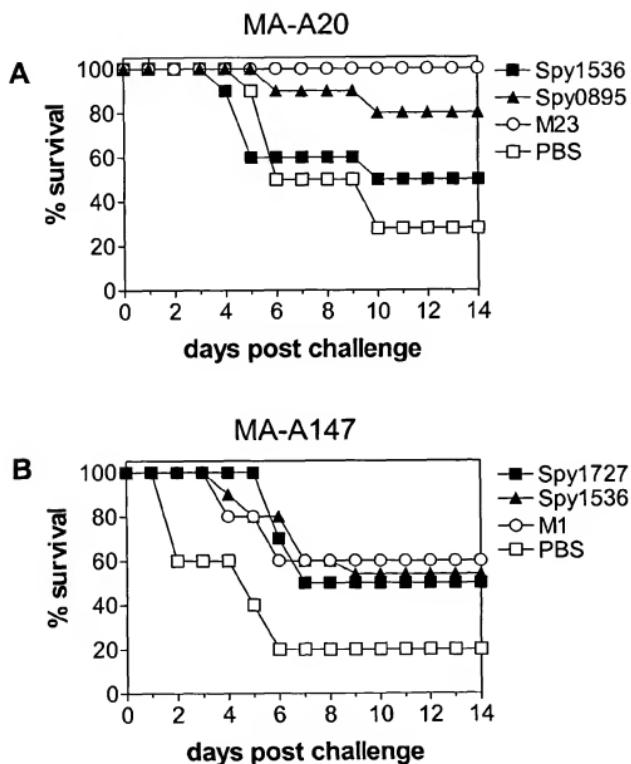
Figure 3**ALUM model**

Figure 4

IC31 i.n. model



INTERNATIONAL SEARCH REPORT

International application No PCT/EP2007/006027

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/032582 A2 (CHIRON CORP [US]; GRANDI GUIDO [US]; TELFORD JOHN [US]; BENSI GIULIANO) 14 April 2005 (2005-04-14) page 26, line 23 – page 53, line 25; claims 2,11,27; sequence 122	1-30



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubt on priority claim(s) or which is used to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *V* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *S* document member of the same patent family

Date of the actual compilation of the international search

18 September 2007

Date of mailing of the international search report

27/11/2007

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Authorized officer

Stoyanov, Borislav

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/EP2007/006027**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.:
because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-30 (only partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 25-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 27-28 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

FURTHER INFORMATION CONTINUED FROM . PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-30 (only partially)

A peptide consisting of SEQ ID NO. 4, or a variant thereof,
the nucleic acid encoding it and the uses thereof.
—

2. claims: 1-30 (only partially)

A peptide consisting of SEQ ID NO. 1, or a variant thereof,
the nucleic acid encoding it and the uses thereof.
—

3. claims: 1-30 (only partially)

A peptide consisting of SEQ ID NO. 2, or a variant thereof,
the nucleic acid encoding it and the uses thereof.
—

4. claims: 1-30 (only partially)

A peptide consisting of SEQ ID NO. 7, or a variant thereof,
the nucleic acid encoding it and the uses thereof.
—

5. claims: 1-30 (only partially)

A peptide consisting of SEQ ID NO. 5, or a variant thereof,
the nucleic acid encoding it and the uses thereof.
—

6. claims: 1-30 (only partially)

A peptide consisting of SEQ ID NO. 6, or a variant thereof,
the nucleic acid encoding it and the uses thereof.
—

7. claims: 1-30 (only partially)

A peptide consisting of SEQ ID NO. 3, or a variant thereof,
the nucleic acid encoding it and the uses thereof.
—

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/006027

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
WO 2005032582	A2	14-04-2005	CA 2532369 A1 EP 1648500 A2 JP 2007500726 T		14-04-2005 26-04-2006 18-01-2007